Καλά ανεκτό προφίλ ασφαλείας του filgotinib και ο μηχανισμός δράσης του

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Ηράκλειο 2023

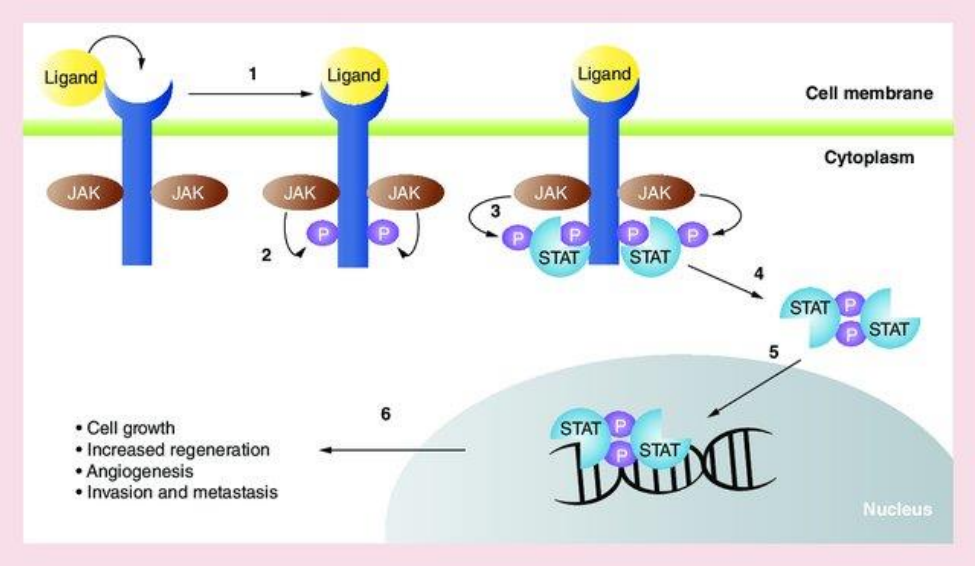
- Conflicts of interest
- Honoraria/speaker grants: Demo, Lilly, Abbvie, Novartis, Janssen, UCB, Pfizer, Aenorasis, Farran,

Janus Kinases (JAK)

What are they?

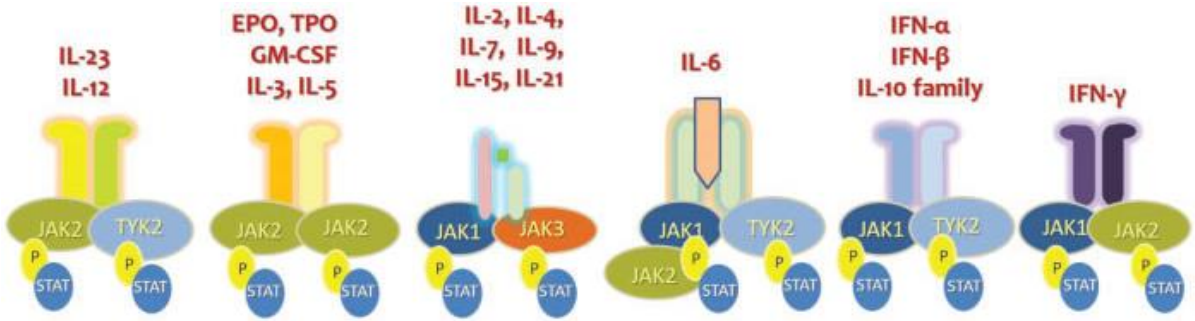
- Just another kinase OR Janus Kinases
- Cytoplasmic tyrosine kinases able to phosphorylate tyrosine residues
  - on themselves (autophosphorylation)
  - on adjacent molecules, including STAT (transphosphorylation)

Janus
God of passages



Tang et al Hep Onc 2020
www. britaanica.com

The JAK/STAT pathway outline

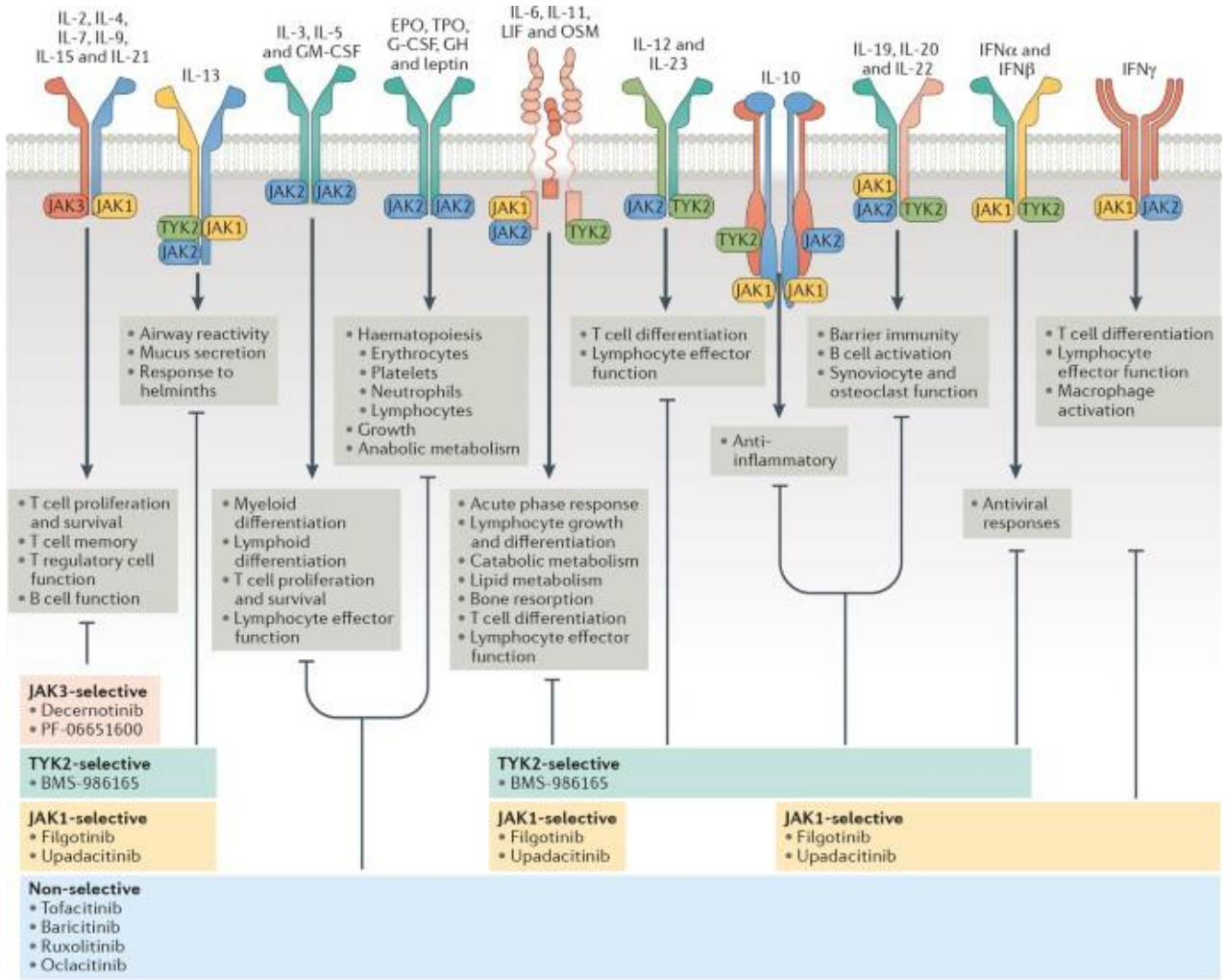


- The JAK/STAT pathway
  - 4 members (JAK1, JAK2, JAK3, TYK) and 7 STAT
- Receptor subunits are associated with a specific JAK
- Many different cytokines may act through the same JAK
  - Inhibiting a JAK molecule may impede more than one pathway
    - Efficacy in multiple immune mediated disease
    - But adverse effects also

Fragoulis G et al Rheumatology (Oxford) 2019
Tanaka Y et al Nat Rev Rheum 2022

JAK-inhibitors

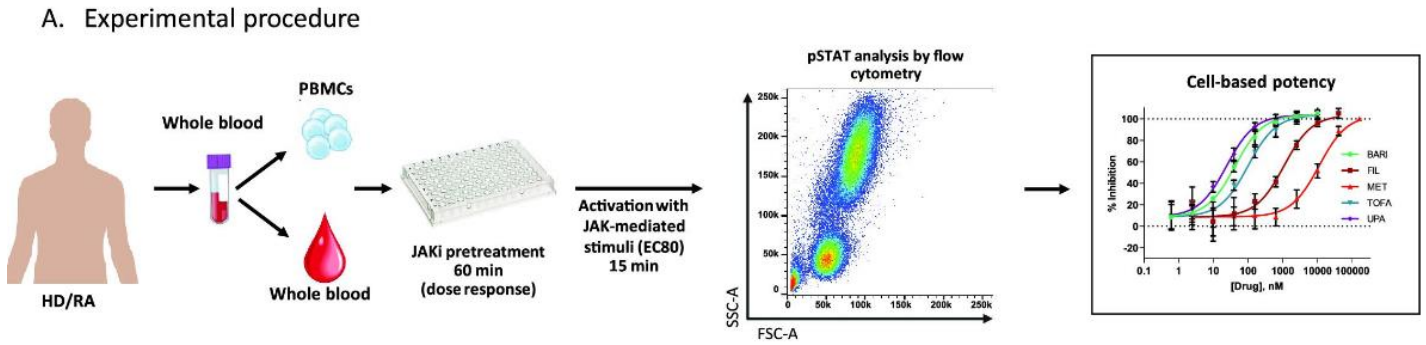
Are they all the same?

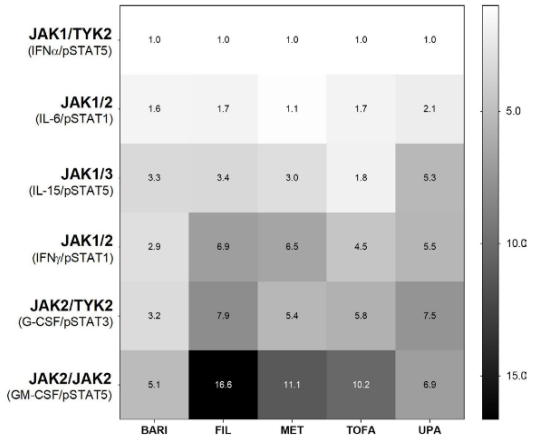


Schwartz et al Nat Rev Drug Disc

JAK-inhibitors Selectivity

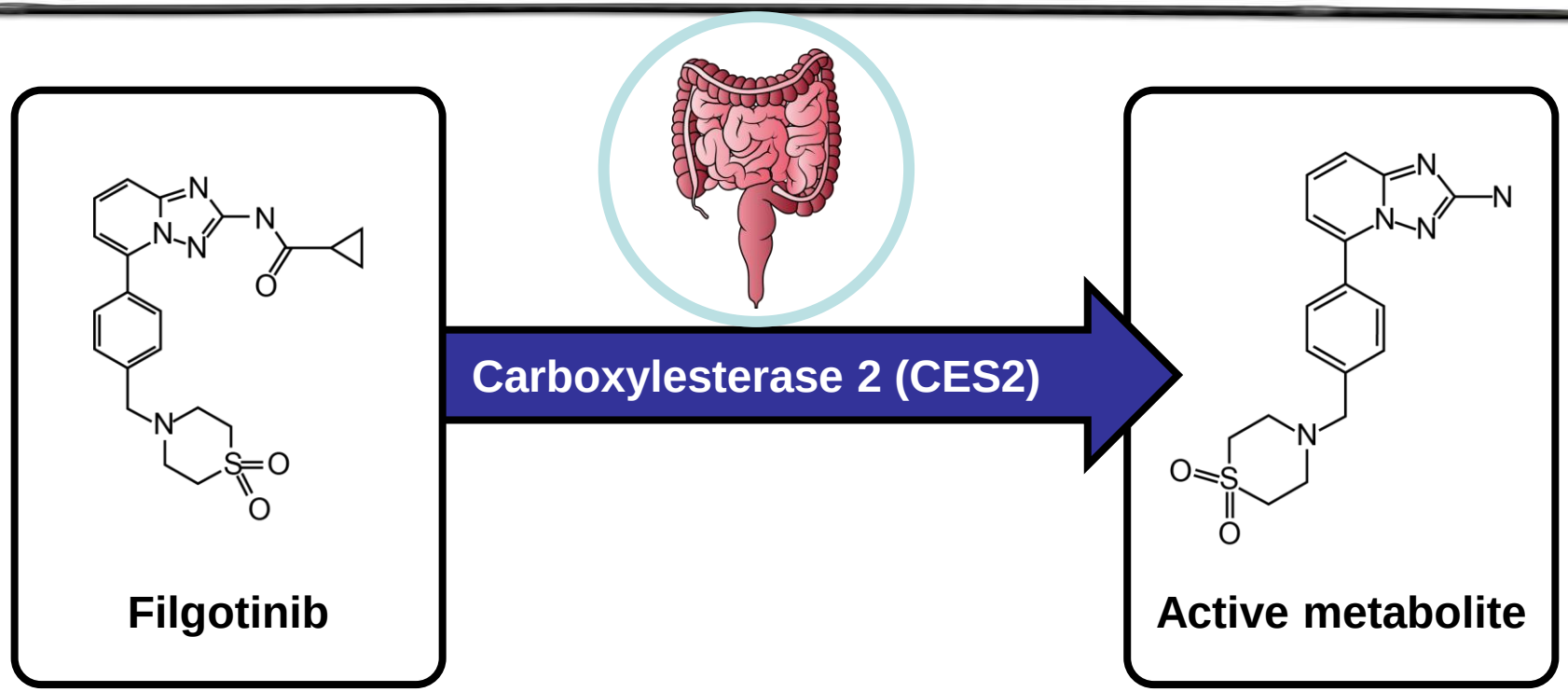
- JAKinibs
  - most potently inhibited the JAK1/TYK2-dependent IFNα/pSTAT5
- Filgotinib and Upadacitinib
  - More selective against JAK2/TYK2
- Filgotinib vs upadacitinib
  - More selective against JAK2





Traves et al. Ann Rheum Dis 2021

Filgotinib is metabolized by CES2 predominantly expressed in the intestine



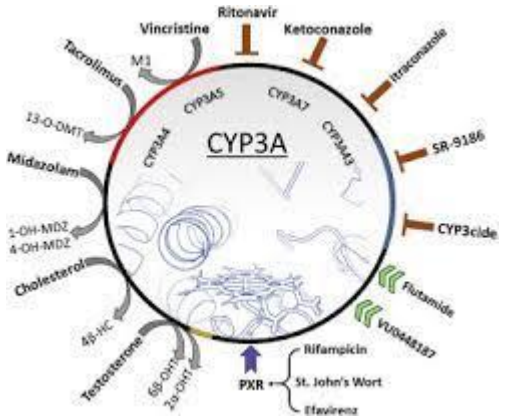
- Filgotinib is metabolized in the intestines via carboxylesterases (CES) to form an active metabolite GS-829845; it is primarily metabolised by CES2, and to a lesser extent by CES1[1]

- Filgotinib is extensively metabolized (~85%) with only 9.4% and 4.5% of an orally administered dose recovered as unchanged filgotinib in urine and faeces, respectively[2]

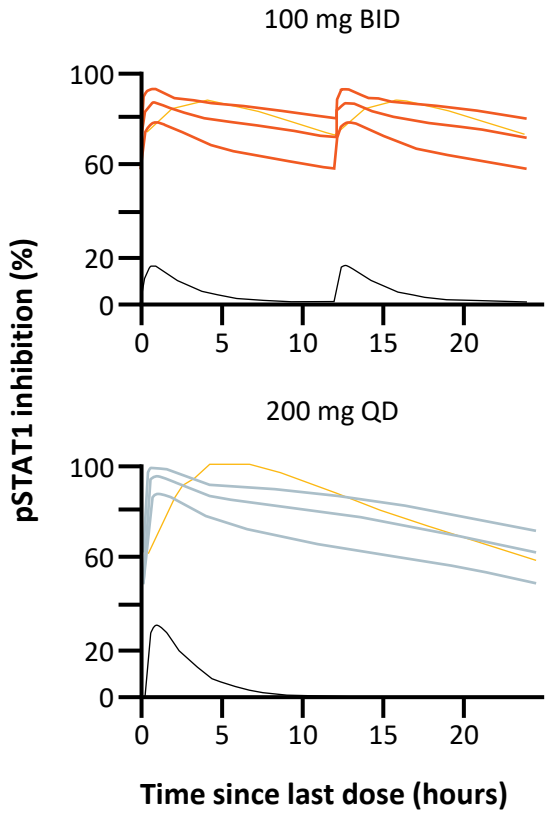
Namour F, *et al. Drug Metabolism Letters 2016*; 10:38–48.

Filgotinib is metabolized by CES2 predominantly expressed in the intestine

- Parent molecule is responsible for early activity (Peak Concentration: 1-3 hours)
- Formation of the active metabolite GS-829845 is responsible for the prolonged duration of activity
- Differs from other JAKi
  - No association with CYP3A4



Simulated steady-state inhibition of pSTAT1[b]



Namour F, et al. Clin Pharmackinet 2015; 54:859–874. 2

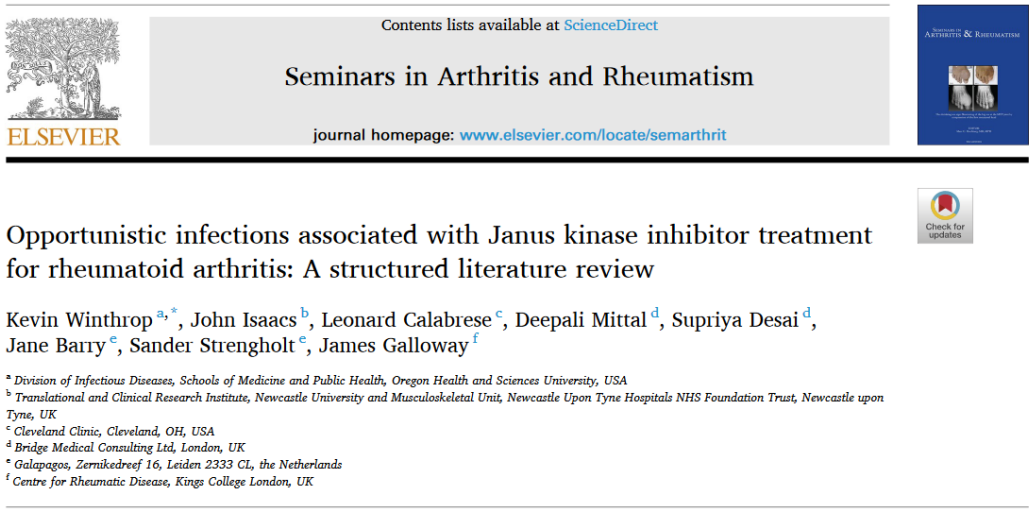
JAK-inhibitors

Safety

- Infections
- Herpes Zoster
- Malignancies
- Cardiovascular

Serious infections

- RA
- 62 RTCs
- No increased signal for Opportunistic infections (apart from HZ)
- Tuberculosis
  - Did not exceed 0.5%



Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Opportunistic infections associated with Janus kinase inhibitor treatment for rheumatoid arthritis: A structured literature review

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[f] Centre for Rheumatic Disease, Kings College London, UK

Serious Infections

- Retrospective study
  - Mutlicentre, Japan
  - RA for 959 patient-years
  - JAK (n=499) vs TNFi (n=203)
  - No risk for serious infections

Table 3. Independent risk factors for infectious diseases other than herpes zoster (HZ) and HZ

Risk factors for serious infectious diseases other than HZ				
Variable	**Univariate model**		**Multivariable model**	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**
Age, >65 yrs or not	1.170 (0.620, 2.210)	0.626		
Disease duration, per 1-yr increase	1.023 (0.993, 1.053)	0.134	1.024 (0.995, 1.054)	0.112
Coexisting diabetes mellitus, yes/no	2.234 (1.137, 4.386)	0.028*	1.922 (0.956, 3.865)	0.067
Concomitant MTX use, yes/no	0.591 (0.319, 1.093)	0.098	0.714 (0.376, 1.358)	0.305
No. of previous use of b/ts DMARDs, per drug	1.031 (0.873, 1.196)	0.848		
Body weight, per 1-kg increase	0.990 (0.962, 1.016)	0.484		
Coexisting lung diseases, yes/no	1.864 (0.976, 3.557)	0.069	1.410 (0.717, 2.770)	0.319
GC use, yes/no	1.658 (0.878, 3.132)	0.113		
GC dose, per 1-mg increase	1.132 (1.044, 1.217)	0.003*	1.105 (1.022, 1.194)	0.012*
Tofacitinib or baricitinib	1.425 (0.644, 3.155)	0.369		

Uchida et al Rheumatology 2023

Serious Infections

- Korea National Health Insurance Service
  - 2009-2019
  - RA starting TNFi (n=5169) or JAKi (n=2963)
  - Fu: 1.16 years
  - Serious infections
    - HR: 1.04 (0.71–1.52)
  - Opportunistic Infections
    - HR: 0.25 (0.09–0.73) (less for JAK)

Choi et al Arthr Res & Ther 2023

JAKi

Herpes Zoster

- Rabbit Registry
  - RA October 2007/2020
  - csDMARDs or bDMARDs or tsDMARDs
- 13 991 patients (62 958 py)
  - with 559 HZ event
- Risk for HZ: 3.6 fold for JAKi
  - (TOF, BARI, UPA)

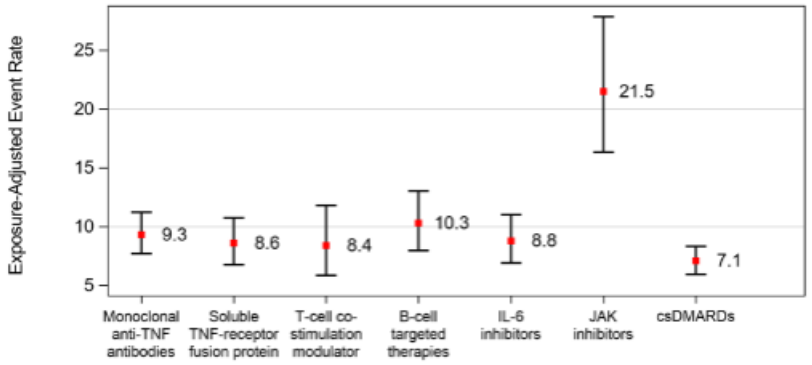


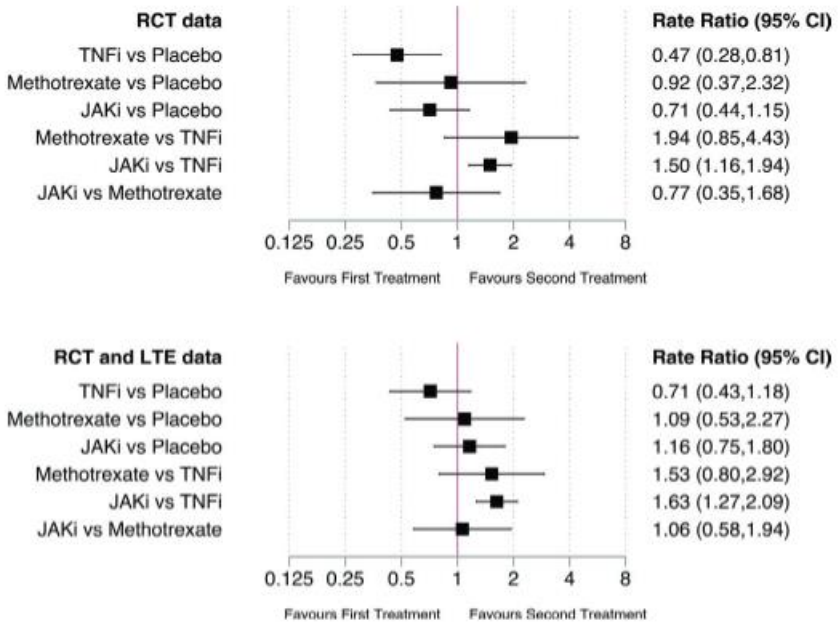
Table 2 Risk of herpes zoster: Andersen-Gill model with and without IPW

	Andersen-Gill model without IPW		Andersen-Gill model with IPW	
Characteristics	**Adjusted HR (95% CI)**	**P value**	**Adjusted HR (95% CI)**	**P value**
Female sex	1.36 (1.10 to 1.68)	**0.0051**	1.13 (0.85 to 1.50)	0.4122
Age per 10 years	1.21 (1.13 to 1.31)	**<0.0001**	1.25 (1.14 to 1.37)	**<0.0001**
Glucocorticoids, 5–10 vs 0 mg/day	1.42 (1.19 to 1.69)	**<0.0001**	1.47 (1.17 to 1.85)	**0.0008**
Glucocorticoids, >10 vs 0 mg/day	3.57 (2.36 to 5.39)	**<0.0001**	4.42 (2.50 to 7.83)	**<0.0001**
csDMARD treatment	*Reference*		*Reference*	
Monoclonal anti-TNF antibodies	1.73 (1.34 to 2.24)	**<0.0001**	1.63 (1.17 to 2.28)	**0.0042**
Soluble TNF receptor fusion protein	1.45 (1.09 to 1.94)	**0.0121**	1.28 (0.90 to 1.81)	0.1687
T cell costimulation modulator	1.25 (0.85 to 1.85)	0.2608	1.45 (0.86 to 2.46)	0.1652
B cell targeted therapy	1.62 (1.21 to 2.18)	**0.0013**	1.57 (1.03 to 2.40)	**0.0355**
IL-6 inhibitors	1.41 (1.06 to 1.89)	**0.0200**	1.44 (0.99 to 2.11)	0.0578
JAK inhibitors	3.23 (2.32 to 4.48)	**<0.0001**	3.66 (2.38 to 5.63)	**<0.0001**

Redeker et al Ann Rheum Dis 2021

Malignancies
JAK Vs TNF

- Network meta-analysis (RCTs &LTEs)
- Across indications
- JAK vs others
  - 62 studies
  - 82.366 person- years of exposure to JAKi, 2924 to placebo, 7909 to TNFi and 1074 to methotrexate.
  - (Effect of ORAL surveillance)



Conclusions: JAKi were associated with a higher incidence of malignancy compared with TNFi but not placebo or methotrexate. Cancers were rare events in all comparisons.

Russell et al Ann Rheum Dis 2023

Malignancies
JAK Vs TNF

- Cohort study (Swedish registry)
  - RA (n=10,447) or PsA (n=4,443)
  - Starting JAK vs TNF Vs non-TNF bDMARDs
- RA
  - Overall: JAK vs TNF; HR was 0.94 (95% CI 0.65 to 1.38)
  - NMSC: : JAK vs TNF; HR was 1.39 (95% CI 1.01 to 1.91)
- PsA
  - Overall: JAK vs TNF; 1.9 (95% CI 0.7 to 5.2)
  - NMSC: JAK vs TNF; 2.1 (95% CI 0.8 to 5.3)

Huss et al Ann Rheum Dis 2023

Malignancies
JAK Vs TNF

- Hong-Kong Biologics registry
- 1732 RA patients follow-up 6431 patient-years
- JAKi (n=551) Vs TNFi (n=1920)
- Similar risk for malignancies

Table 4. Hazard ratios for MACEs, cancers and infections of the JAK relative to the TNF inhibitors

	Univariate HR (95% CI)	*P*	Multivariate HR (95% CI)	*P*
MACEs	2.09 (1.10, 3.95)	0.02	1.36 (0.62, 2.96)[a]	0.44
Cancers	0.84 (0.39, 1.83)	0.66	0.87 (0.39, 1.95)[b]	0.74
Infections	1.43 (1.16, 1.77)	0.001	1.08 (0.84, 1.39)[c]	0.55

[a] Adjusted for age, sex, RA duration, smoking, BMI, past MACE and vascular risk factors that required therapies.
[b] Adjusted for age, sex, RA duration, smoking, past history of cancer and use of concomitant csDMARDs.
[c] Adjusted for age, sex, RA duration, diabetes mellitus and the use of concomitant csDMARDs (including GCs). csDMARDs: conventional DMARDs; GC: glucocorticoids; HR: hazard ratio; MACEs: major adverse cardiovascular events.

Huss et al Ann Rheum Dis 2023

JAK
Malignancies

- Hypothesis
  - JAKinibs might affect NK proliferation and tumour lysing capacity
- NK cells were isolated from healthy PBMC
  - incubated in vitro with 8 concentrations of each evaluated JAKinib (TOFA, BARI, FIL, FIL metabolite, UPA)
  - stimulated with IL-15 for proliferation or IL-12/18 for IFNγ production.
- dose-dependent inhibition of IL-15-induced proliferation for all JAKi
  - TOFA>UPA>BARI≈FIL

Traves P et al Ann Rheum Dis 2021
Noctrune et al Cell Mol Immun 2020

JAKinibs

MACE & VTE (what we know so far…)

Author-Year	Disease (N)	Comparators	Data source	Adjustments	Outcome HR (95% CI)
Desai et al-2022	RA (87,653)	tofacitinib Vs TNFi	MarketScan Medicare Optum	Demographics, Comorbidities, RA-related medication, other co-medication	**VTE** 1.13 (0.77–1.65)
Hoisnard et al-2022	RA (15,835)	tofacitinib, baricitinib Vs adalimumab	French national health data system	Demographics, social, comorbidities, CV-risk factors, RA-related medication, antiplatelet or anticoagulant Drugs	**MACE** 1.0 (0.7-1.5) **VTE** 1.1 (0.7-1.6)
Khosrow-Khavar et al-2022	RA (RWS: 102,263) (RCT-duplicate: 35,070)	tofacitinib Vs TNFi	Optum Clinformatics, IBM MarketScan Medicare	Demographics, healthcare resource utilization comorbidities, CV-related variables, RA-related medication, other co-medications	**Composite CV outcome*** 1.01 (0.83-1.23) in RWS 1.24 (0.90-1.69) in RCT-duplicate cohort
Kremer et al-2021	RA (10,357)	Tofacitinib vs bDMARDs	US Corrona RA registry	Demographics, social, past medication history, MACE history, RA-related features, RA-related treatments	**MACE** 0.61 (0.34-1.06)
Molander et al-2022	RA (32,737)	Tofacitinib, baricitinib Vs TNFi or non-anti-TNF bDMARDs	Swedish Rheumatology Quality Register was linked to national health registers	Demographics, social, comorbidities, RA-related features including disease activity, RA-related medication,	**VTE** 1.73 (1.24-2.42) **PE** 3.21 (2.11-4.88) **DVT** 0.83 (0.47-1.45)
Ytterberg et al-2022	RA (4,362)	Tofacitinib¶ vs TNFi (adalimumab, etanercept)	ORAL Surveillance	Not reported	**MACE** 1.24 (0.81–1.91) **VTE** 1.66 (0.76–3.63)
Salinas et al-2022	RA (15.212)	Baricitinib vs TNFi	14 real-world data sources	demographics, comorbidities, medical history, RA-related treatment	**MACE** **1.54 (95% CI 0.93, 2.54)** **VTE** **1.51 (95% CI 1.10, 2.08)**

Evangelatos & Fragoulis Clin Rheum 2022

JAKinibs

MACE & VTE

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

These medicines (Xeljanz, Cibinqo, Olumaint, Rinvoq and Jyseleca) should only be used in the following patients if no suitable treatment alternatives are available: those aged 65 years or above, those who are current or past long-time smokers, those with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors, or those with other malignancy risk factors. Cautious use is also recommended in patients with known risk factors for VTE other than those listed above.

For PsA

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

4. 4. In patients with peripheral arthritis and an inadequate response to at least one csDMARD, therapy with a bDMARD should be commenced.
5. In patients with peripheral arthritis and an inadequate response to at least one bDMARD, or when a bDMARD is not appropriate, a JAKi may be considered, taking safety considerations* into account.

Add a bDMARD[5];
Consider use of a
JAK-inhibitor
only after risk assessment[6]

The following risk factors for cardiovascular events and malignancies must be considered when intending to prescribe a JAK-inhibitor: Age over 65 years, history of current or past smoking, other cardiovascular risk factors (such as diabetes, obesity, hypertension), other risk factors for malignancy (current or previous history of malignancy other than successfully treated NMSC), risk factors for thromboembolic events (history of MI or heart failure, cancer, inherited blood clotting disorders or a history of blood clots, as well as patients taking combined hormonal contraceptives or hormone replacement therapy, undergoing major surgery or immobile)

Filgotinib RA integrated safety analysis across 7 studies

7 Pooled data across seven Phase 2 and Phase 3 studies[1]

Phase 3 studies

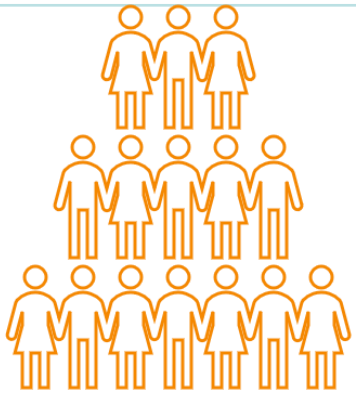
FINCH 1 | MTX-IR[2]
FINCH 2 | Biologic-IR[3]
FINCH 3 | MTX-naïve[4]
FINCH 4 | Long-term extension*[1]

Phase 2 studies[1]

DARWIN 1
DARWIN 2
DARWIN 3 | Long-term extension†

Patients with RA who received >1 dose of treatment

Safety analysis sets[1]	PBO controlled (12 weeks)		ADA controlled (52 weeks)		MTX controlled (52 weeks)		As treated	
	N	PYE	N	PYE	N	PYE	N	PYE
FIL 200 mg QD	777	179.8	475	439.7	626	578.9	2227	3079.2
FIL 100 mg QD	788	181.6	480	443.4	207	195.0	1600	1465.3
PBO	781	178.4	-	-	-	-	-	-
ADA	-	-	325	297.5	-	-	-	-
MTX	-	-	-	-	461	372.2	-	-



4057 Patients[1]

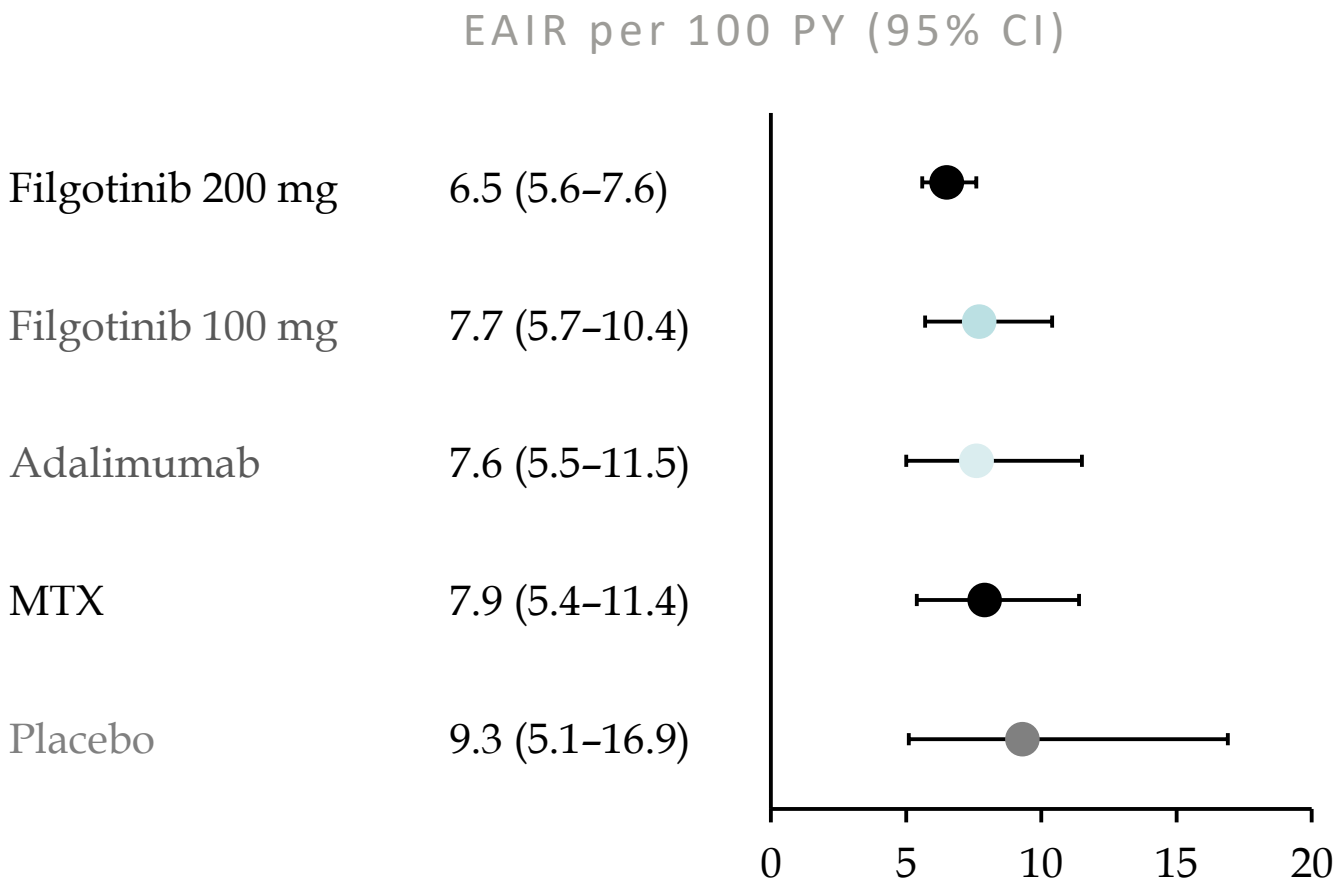
5493 Total PY of exposure[1]

*Data as of March 2019.1 †Data as of May 2018.
ADA: adalimumab; FIL: filgotinib; IR: insufficient responder; N: number of patients; MTX: methotrexate; PBO: placebo; PY: patient-year; PYE: patient-year exposure; QD: once daily; RA: rheumatoid arthritis

References: 1. Genovese EULAR 2020 (THU0202). 2.Combe B. Ann Rheum Dis 2021;80:848–858. 3.Genovese. J*AMA.* 2019;322(4):315–325. 4. Westhovens. Ann Rheum Dis 2021;80:727-738,

Integrated safety analysis across 7 studies

Treatment-emergent serious adverse events

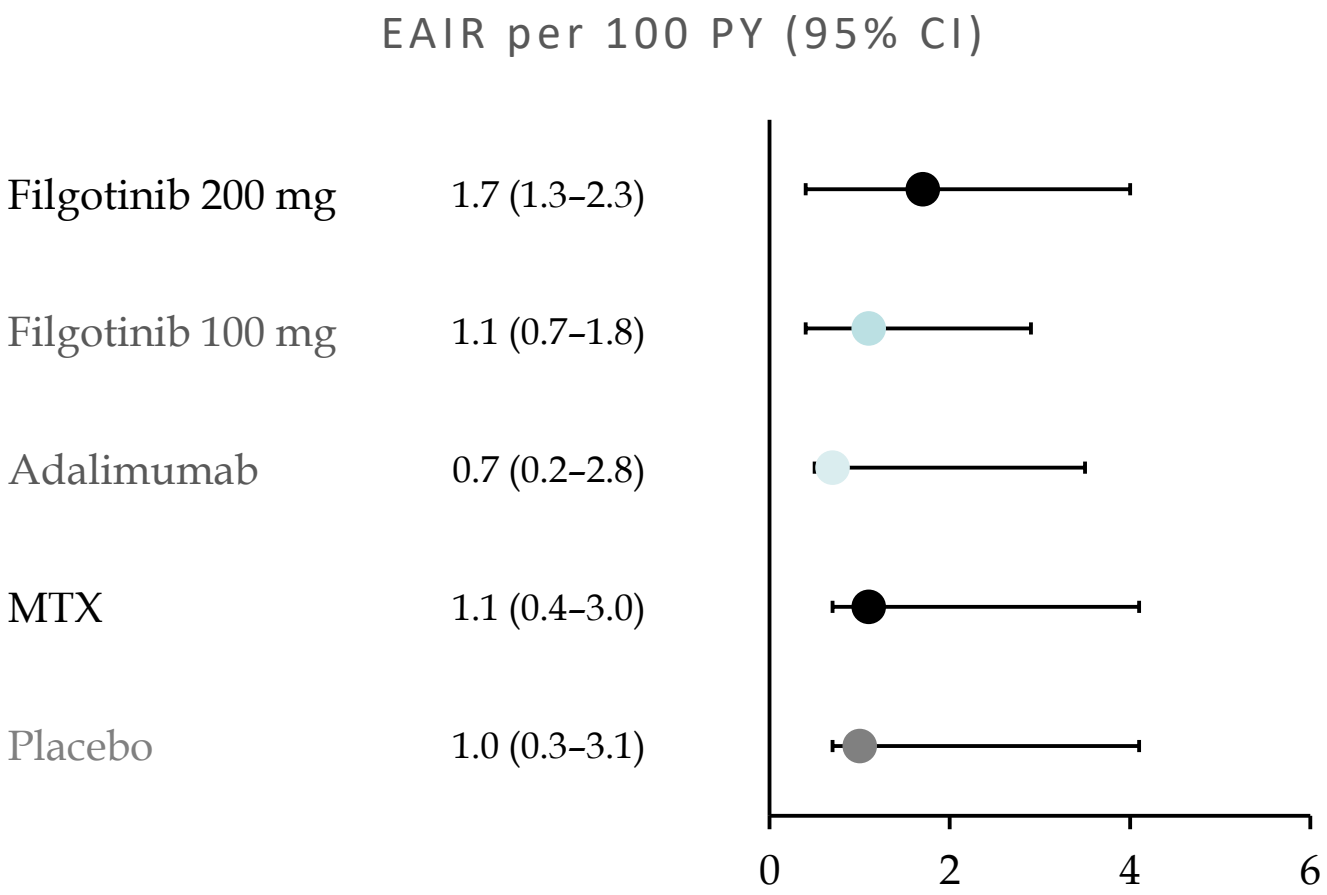


- Exposure-adjusted incidence rates (EAIRs) of TEAEs were **similar for FIL 100 mg and FIL 200 mg vs. ADA and MTX**.
- The **most common infections** in the FIL total group (>10% patients) were nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, and influenza.

References: Genovese EULAR 2020 THU0202. Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

Integrated safety analysis across 7 studies

Herpes zoster



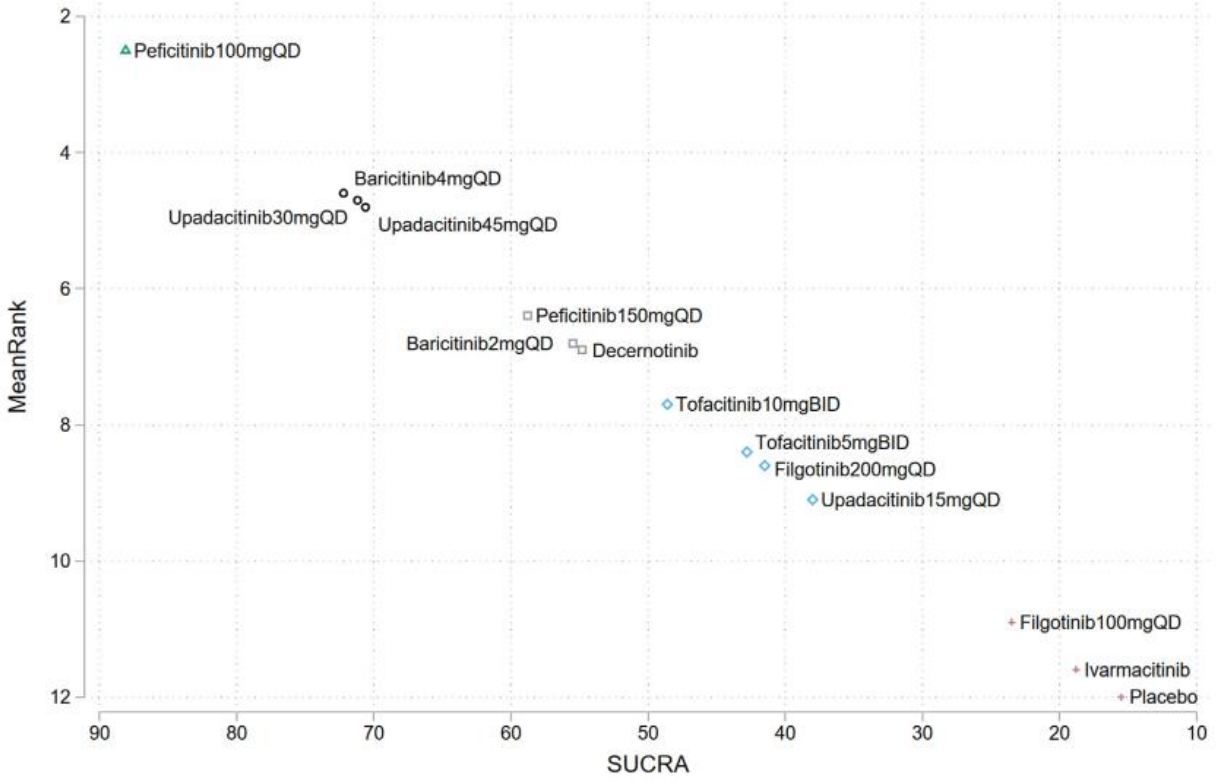
- The EAIR for **herpes zoster** for FIL was **low overall** and similar to MTX, but numerically higher relative to placebo and ADA.

References: Genovese EULAR 2020 THU0202. Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

JAKi

Hepres Zoster – Metaanalysis

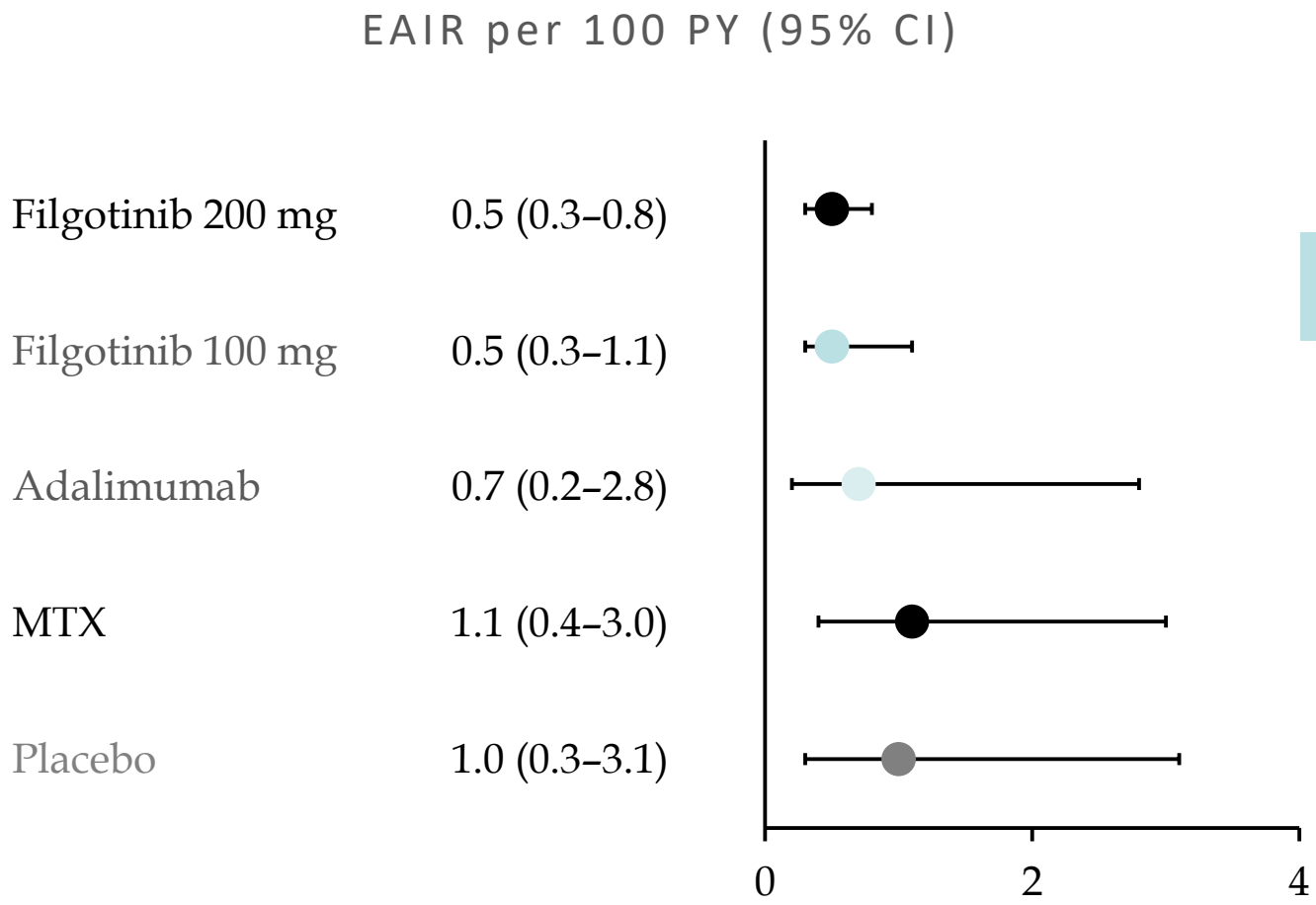
- Network meta-analysis
  - 47 RCTs, 24.142 patients
  - Subgroup analysis performed
    - Indication
    - Drug
  - Higher risk for
    - Peficitinib>Baricitinib>Upadacitinib30 mg
    - More pronounced in RA



Xu et al Front Pharm 2023

Integrated safety analysis across 7 studies

Malignancies (excluding NMSC)

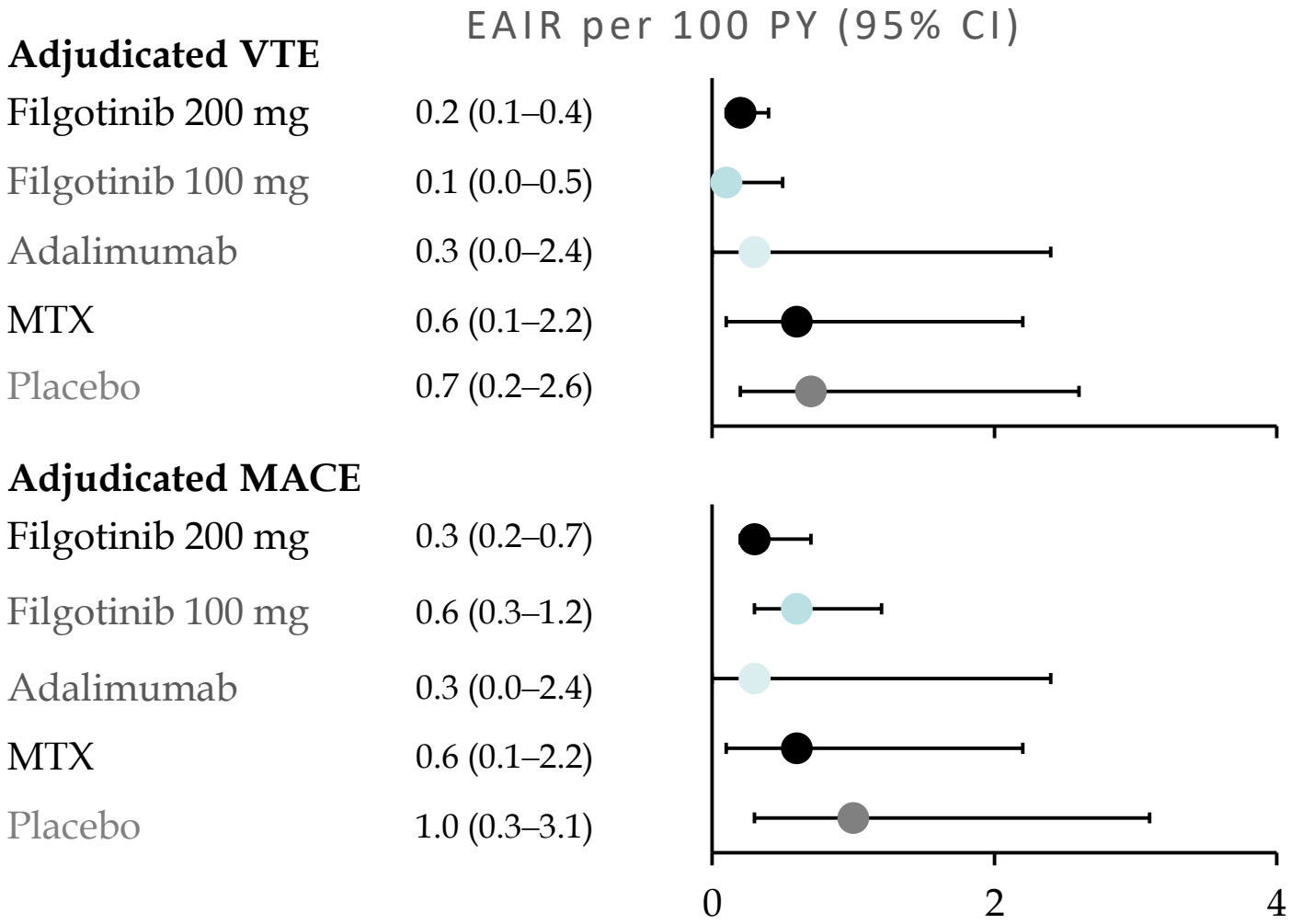


- **Malignancies were rare overall**, and rates were low in patients receiving FIL.

References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

Integrated safety analysis across 7 studies

VTE and MACE



- **Events of MACE and VTE with FIL were uncommon** and numerically low compared to placebo.

References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

Adverse reactions

Most common reported adverse reactions:

- Nausea (3.5%), upper respiratory tract infection (3.3%), urinary tract infection (1.7%) and dizziness (1.2%)

Overview of adverse reactions*

	COMMON (≥1/100 - <1/10)	UNCOMMON (<1/100)
Infections and infestations	Urinary tract infection Upper respiratory tract infection	Herpes zoster Pneumonia
Blood and lymphatic system disorders		Neutropenia
Metabolism and nutrition disorders		Hypercholesterolaemia
Nervous system disorders	Dizziness	
Gastrointestinal disorders	Nausea	
Investigations		Blood creatine phosphokinase increased

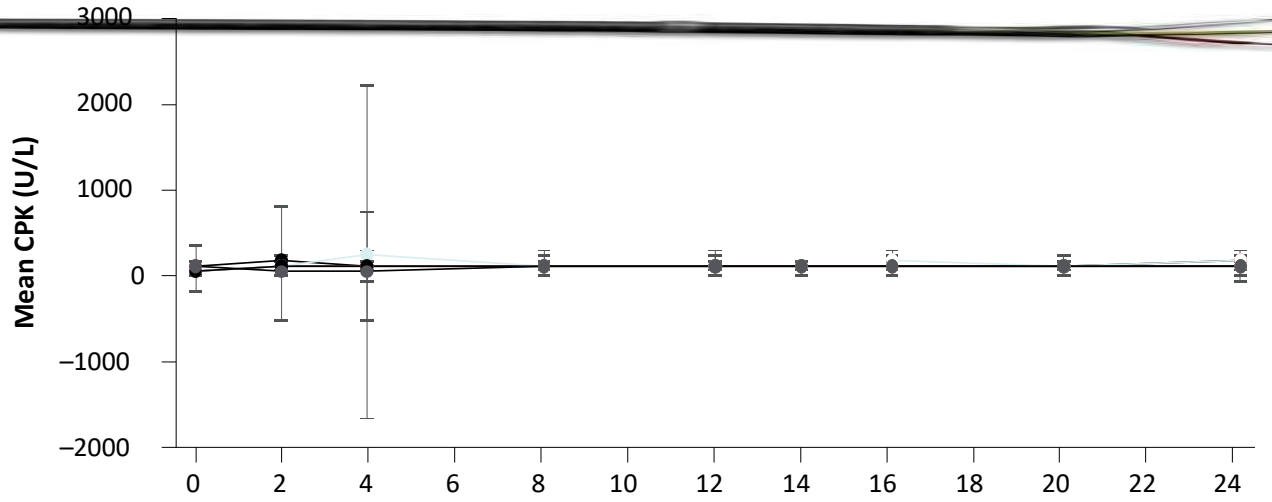
***** Frequency based on placebo-controlled pre-rescue period (week 12) pooled across FINCH 1 and 2, and DARWIN 1 and 2, for patients who received filgotinib 200 mg.

References: Filgotinib – SmPC 25 September 2020

Laboratory parameters

Creatine phosphokinase

- In FINCH 1, 2 and 3 studies, dose-dependent increases in median creatine kinase were observed in the FIL groups.
- Median values in all treatment groups were **within the normal laboratory reference range over time**.



Creatine phosphokinase (CK) elevation

Grade 1: increase of creatine phosphokinase of greater than ULN to 2.5 x ULN

Grade 2: increase of creatine phosphokinase of greater than 2.5 x ULN to 5 x ULN

Grade 3: increase of creatine phosphokinase of greater than 5 x ULN to 10 x ULN

Grade 4: increase of creatine phosphokinase of greater than 10 x ULN

Creatine Kinase (Increased), n (%)	PBO+MTX / csDMARD N=1031	ADA 40 mg + MTX N=324	FIL 100mg + MTX/ csDMARD N=835	FIL 200mg + MTX/ csDMARD N=1034	FIL 200 MONO N=207	FIL total N=2078
Any Grade 1 or Higher	91 (8,8)	42 (13,0)	131 (15,7)	266 (25,7)	59 (28,5)	456 (22,0)
Grade 1	76 (7,4)	38 (11,7)	115 (13,8)	234 (22,6)	45 (21,7)	394 (19,0)
Grade 2	10 (1,0)	3 (0,9)	9 (1,1)	23 (2,2)	11 (5,3)	43 (2,1)
Grade 3	5 (0,5)	1 (0,3)	4 (0,5)	4 (0,4)	2 (1,0)	10 (0,6)
Grade 4	0	0	3 (0,4)	5 (0,5)	1 (0,5)	9 (0,4)

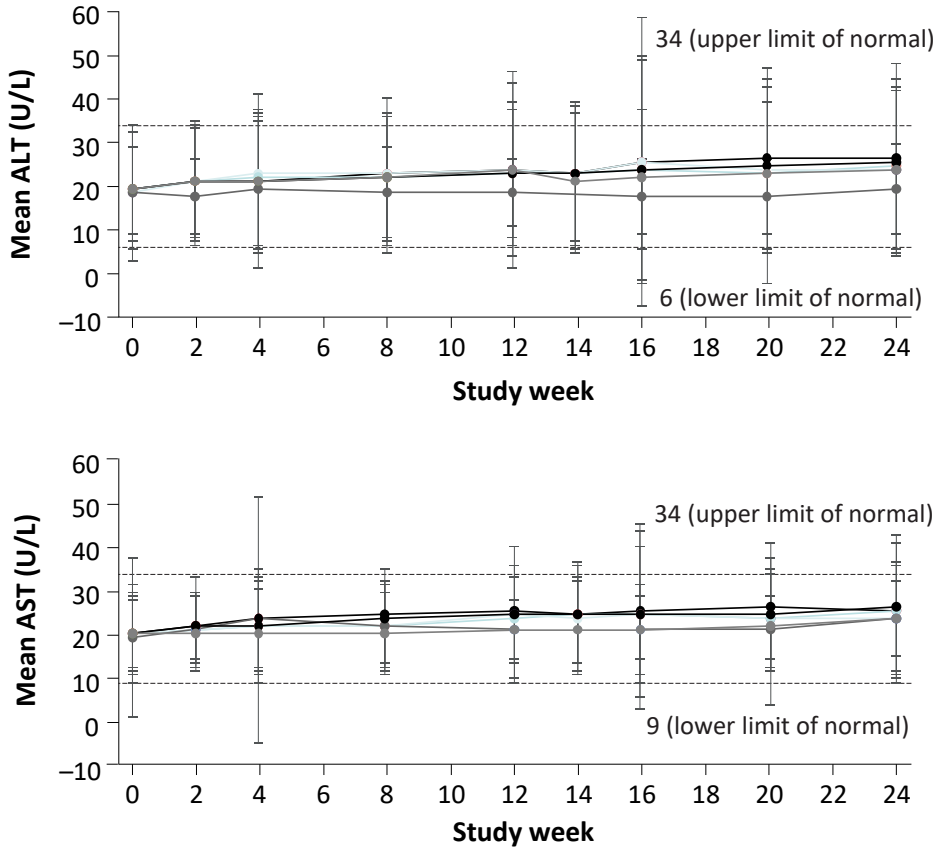
Severity grades were defined by the CTCAE version 4.03.

References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

Laboratory parameters

ALT and AST

In the FINCH studies, the incidence of Grade 3 toxicities with FIL monotherapy was lower than FIL+MTX and ADA+MTX. **Grade 3 and 4 ALT abnormalities were similar among all treatment arms**.



ALT, n (%)	PBO+MTX/ csDMARD N=1031	ADA 40 mg + MTX N=324	FIL 100mg + MTX/ csDMARD N=835	FIL 200mg + MTX/ csDMARD N=1034	FIL 200 MONO N=207	FIL total N=2078
Any Grade 1 or Higher	250 (24,2)	103 (31,8)	218 (26,1)	287 (27,8)	33 (15,9)	538 (25,9)
Grade 1	217 (21,0)	89 (27,5)	195 (23,4)	239 (23,1)	31 (15,0)	465 (22,4)
Grade 2	26 (2,5)	8 (2,5)	16 (1,9)	31 (3,0)	1 (0,5)	48 (2,3)
Grade 3	7 (0,7)	6 (1,9)	7 (0,8)	17 (1,6)	1 (0,5)	25 (1,2)
Grade 4	0	0	0	0	0	0
AST, n (%)						
Any Grade 1 or Higher	191 (18,5)	80 (24,7)	189 (22,6)	261 (25,2)	33 (15,9)	483 (23,3)
Grade 1	182 (17,7)	75 (23,1)	177 (21,2)	235 (22,7)	31 (15,0)	443 (21,3)
Grade 2	8 (0,8)	3 (0,9)	9 (1,1)	18 (1,7)	0	27 (1,3)
Grade 3	1 (<0,1)	2 (0,6)	3 (0,4)	8 (0,8)	2 (1,0)	13 (0,6)
Grade 4	0	0	0	0	0	

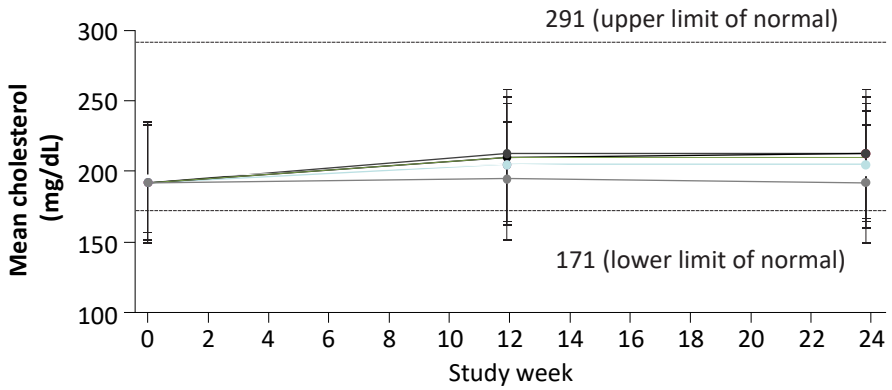
Severity grades were defined by the CTCAE version 4.03. Dashed lines represent the female upper and lower limits of normal.

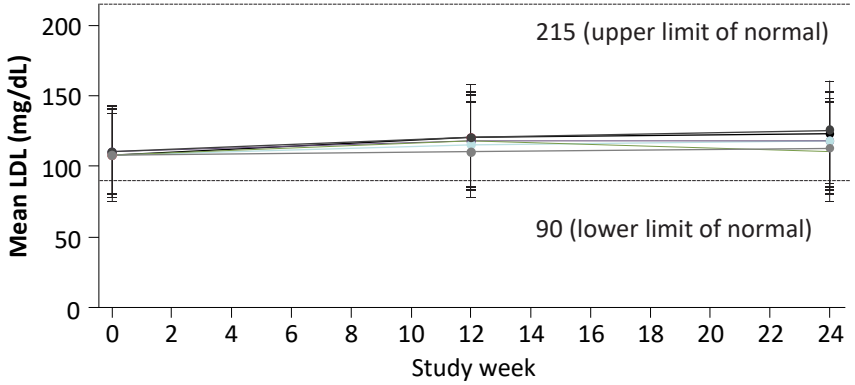
References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

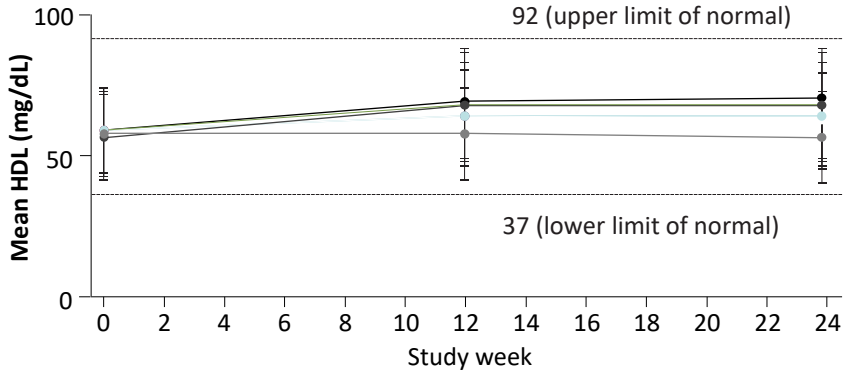
Laboratory parameters

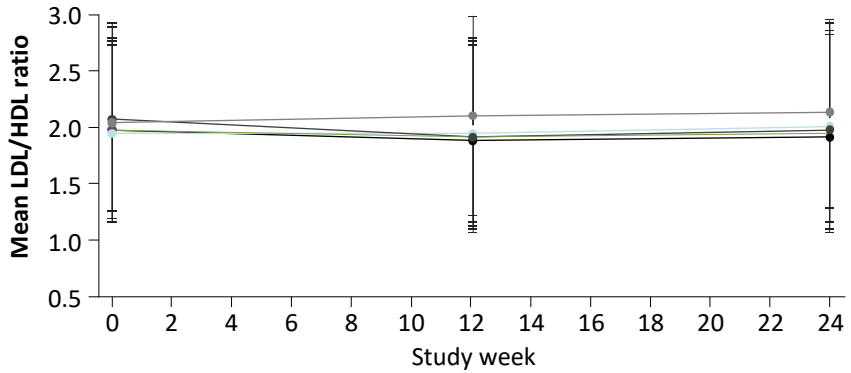
Lipids (fasting)

- For all treatment groups, **LDL remained stable** across the 24-week study periods
- **HDL slightly increased** for patients receiving FIL and ADA
- The **LDL/HDL ratio** remained **stable** for all treatment groups.









- PBO + MTX/csDMARD
- ADA 40 mg + MTX
- FILGO 100 mg + MTX/csDMARD
- FILGO 200 mg monotherapy
- FILGO 200 mg + MTX/csDMARD
- FILGO Total

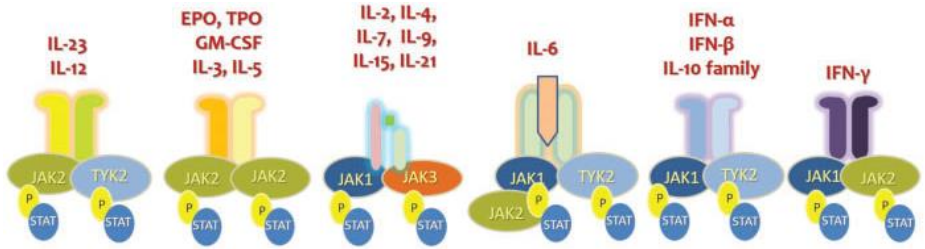
Severity grades were defined by the CTCAE version 4.03. Dashed lines represent the female upper and lower limits of normal.

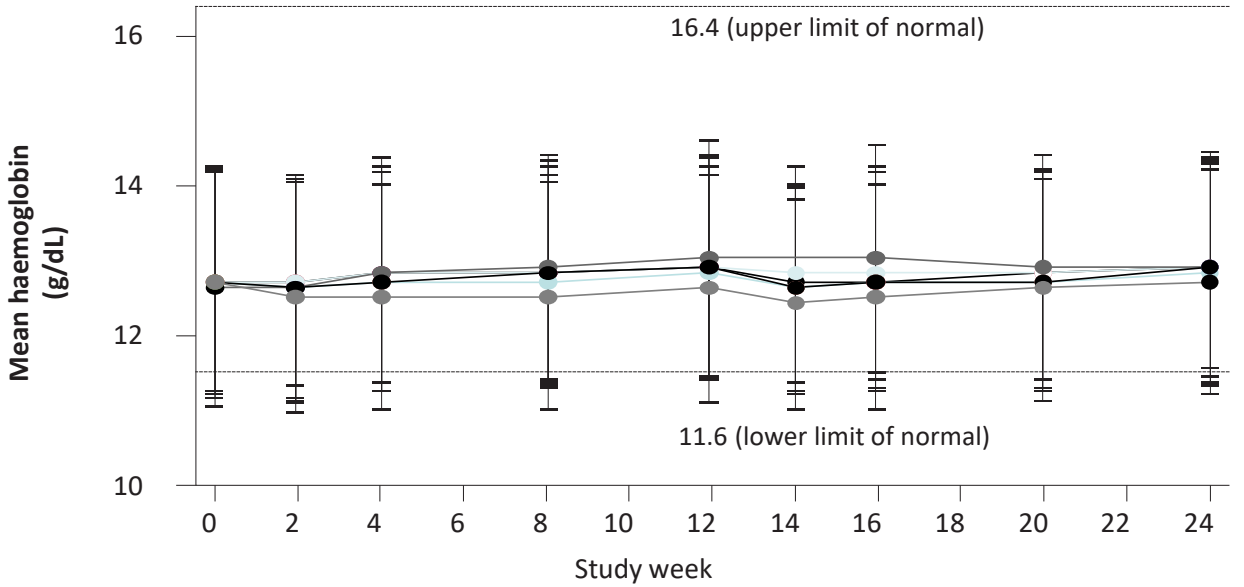
References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

Laboratory parameters

Haemoglobin

- **Mean hemoglobin** slightly increased for patients receiving FIL and ADA.
- A higher frequency of **Grade 3 decreases in haemoglobin** was observed in **patients receiving PBO plus MTX/csDMARDs**.





Hemoglobin (anemia), n (%)	PBO+MTX / csDMARD N=1030	ADA 40 mg + MTX N=324	FIL 100mg + MTX/ csDMARD N=835	FIL 200mg + MTX/ csDMARD N=1034	FIL 200 MONO N=207	FIL total N=2076
Any Grade 1 or Higher	267 (25,9)	51 (15,7)	164 (19,6)	195 (18,9)	33 (15,9)	392 (18,9)
Grade 3	10 (1,0)	2 (0,6)	4 (0,5)	7 (0,7)	0	11 (0,5)

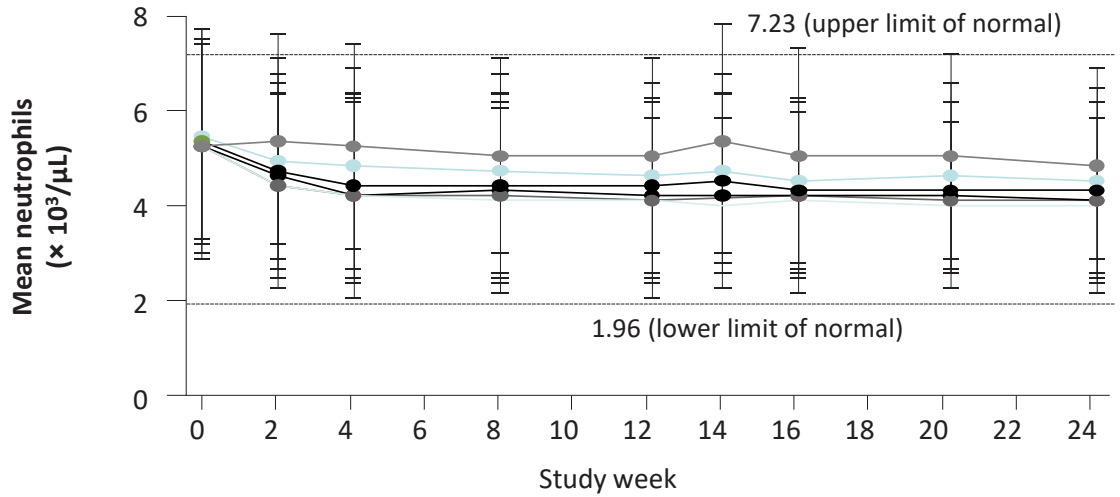
Severity grades were defined by the CTCAE version 4.03. Dashed lines represent the female upper and lower limits of normal.

References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021

Haematology parameters

Neutrophils

- Neutrophil counts **remained stable** across the 24-week study period.
- There was a small increase in the incidence of Grade 3 and 4 neutropenia in patients receiving FIL.



Neutropenia in RA
About 7%
Mild, transient, not associated with infections rate

Neutrophils decreased, n (%)	PBO+MTX/ csDMARD N=1301	ADA 40 mg + MTX N=324	FIL 100mg + MTX/ csDMARD N=835	FIL 200mg + MTX/ csDMARD N=1034	FIL 200 MONO N=207	FIL total N=2076
Any Grade 1 or Higher	67 (6,5)	66 (20,4)	76 (9,1)	146 (14,1)	26 (12,6)	248 (11,9)
Grade 1	50 (4,9)	45 (13,9)	52 (6,2)	93 (9,0)	16 (7,7)	161 (7,8)
Grade 2	13 (1,3)	20 (6,2)	17 (2,0)	45 (4,4)	8 (3,9)	70 (3,4)
Grade 3	4 (0,4)	1 (0,3)	6 (0,7)	8 (0,8)	1 (0,5)	15 (0,7)
Grade 4	0	0	1 (0,1)	0	1 (0,5)	2 (<0,1)

Severity grades were defined by the CTCAE version 4.03. Dashed lines represent the female upper and lower limits of normal.

References: Winthrop KL. Ann Rheum Dis Epub ahead of print: Nov 2021
Fragoulis et al RMD Open 2018

Safety in special populations

Mild**: no dose adjustment is required.
Moderate-severe**: 100 mg once daily is recommended.

FIL has not been studied in patients with **end-stage renal disease**** and is not recommended in these patients.

Mild-moderate*: no dose adjustment is required.

FIL has **not been studied in subjects with severe*** hepatic impairment and is not recommended in these patients.

Age ≥75 years is associated with a higher incidence of serious infections.

A starting dose of 100 mg QD is recommended for patients ≥75 years as clinical experience is limited.

In **animal studies**, decreased fertility, impaired spermatogenesis, and histopathological effects on male reproductive organs were observed.
At the no-observed-adverse-effect-levels in dogs (the most sensitive species), the exposure margin is 2.7-fold at the 200 mg once daily dose in humans.
Male patients should be informed on the potential risk of reduced fertility or infertility before initiating treatment.

Not studied in children under the age of 18 years.

* Mild hepatic impairment: Child Pugh A; moderate hepatic impairment: Child Pugh B; severe hepatic impairment: Child Pugh C
** Mild renal impairment: creatinine clearance ≥60 mL/min; moderate or severe: creatinine clearance 15 to <60 mL/min; end stage renal disease: creatinine clearance <15 mL/Min

References: Filgotinib – SmPC December 2021

Any problem with male fertility?

Probably not

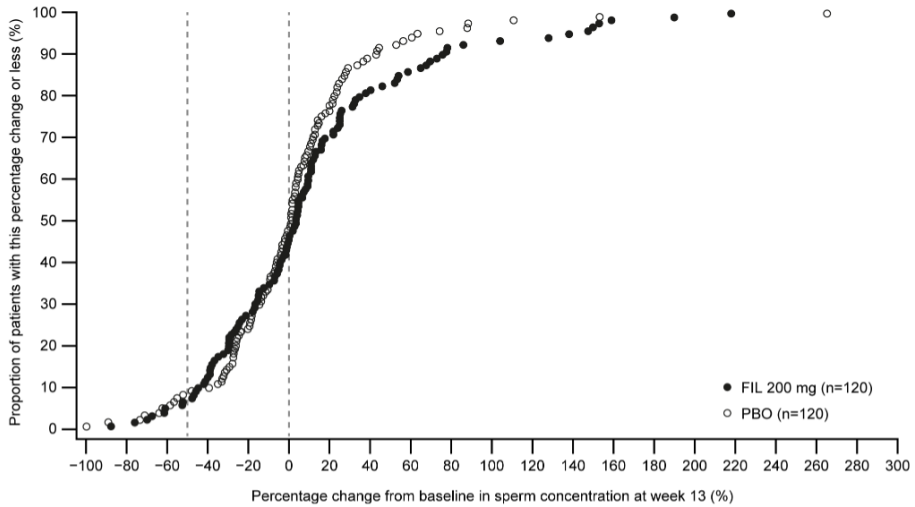
- MANTA (NCT03201445) and MANTA- Ray (NCT03926195)
  - Men (21–65 years) with IBD and RA/SpA/PsA
  - Normal semen parameters at baseline
  - 1:1 Filgo OR PBO for 13 weeks
  - Primary endpoint: % of pts with ≥50% decrease from baseline in sperm concentration at week 13
    - Those met the primary endpoint were monitored over an additional 52 weeks for 'reversibility'.
  - Secondary endpoints included
    - Change from baseline to week 13 in: sperm concentration, total motility, normal morphology, total count and ejaculate volume
  - Exploratory endpoints: sex hormones levels

Reinisch et al Ann Rheum Dis 2023

Any problem with male fertility?

Probably not

- 248 pts were randomized
- Very Reassuring results
- Similar % of filgotinib-treated versus placebo-treated patients met the primary endpoint
- No differences
  - Secondary endpoints
  - Exploratory endpoints
- Results found in rats/dogs were not reproduced in humans



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Conclusions

- Selective JAKi inhibitor
  - Not another brick in the wall…..
- No New safety signals
  - No signal so far for MACE/VTE
  - No signal so far for malignancies
  - Possibly better in terms of HZ
  - Safe in every-day practice

Thank you for your attention ☺

Please remember ☺