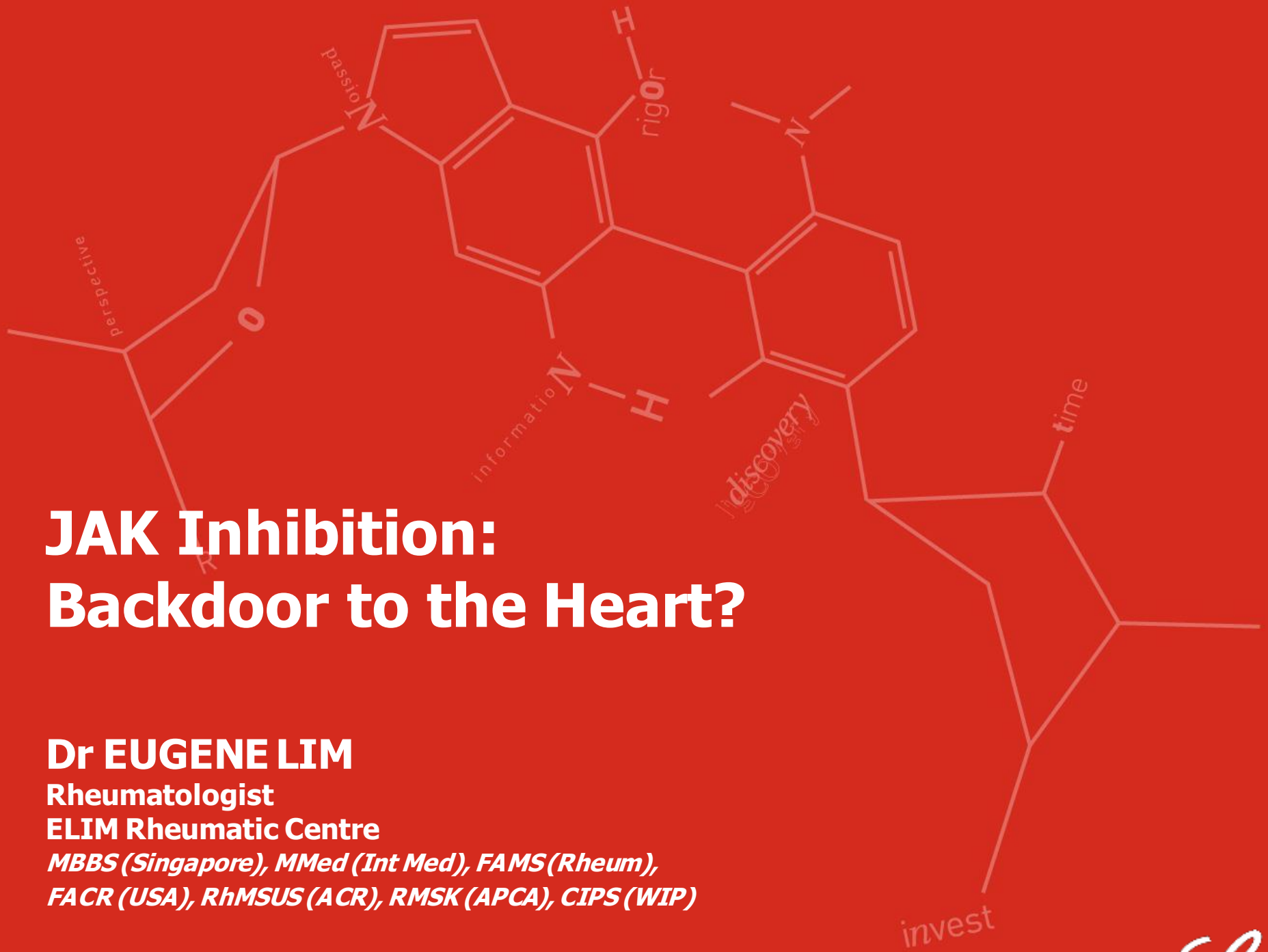
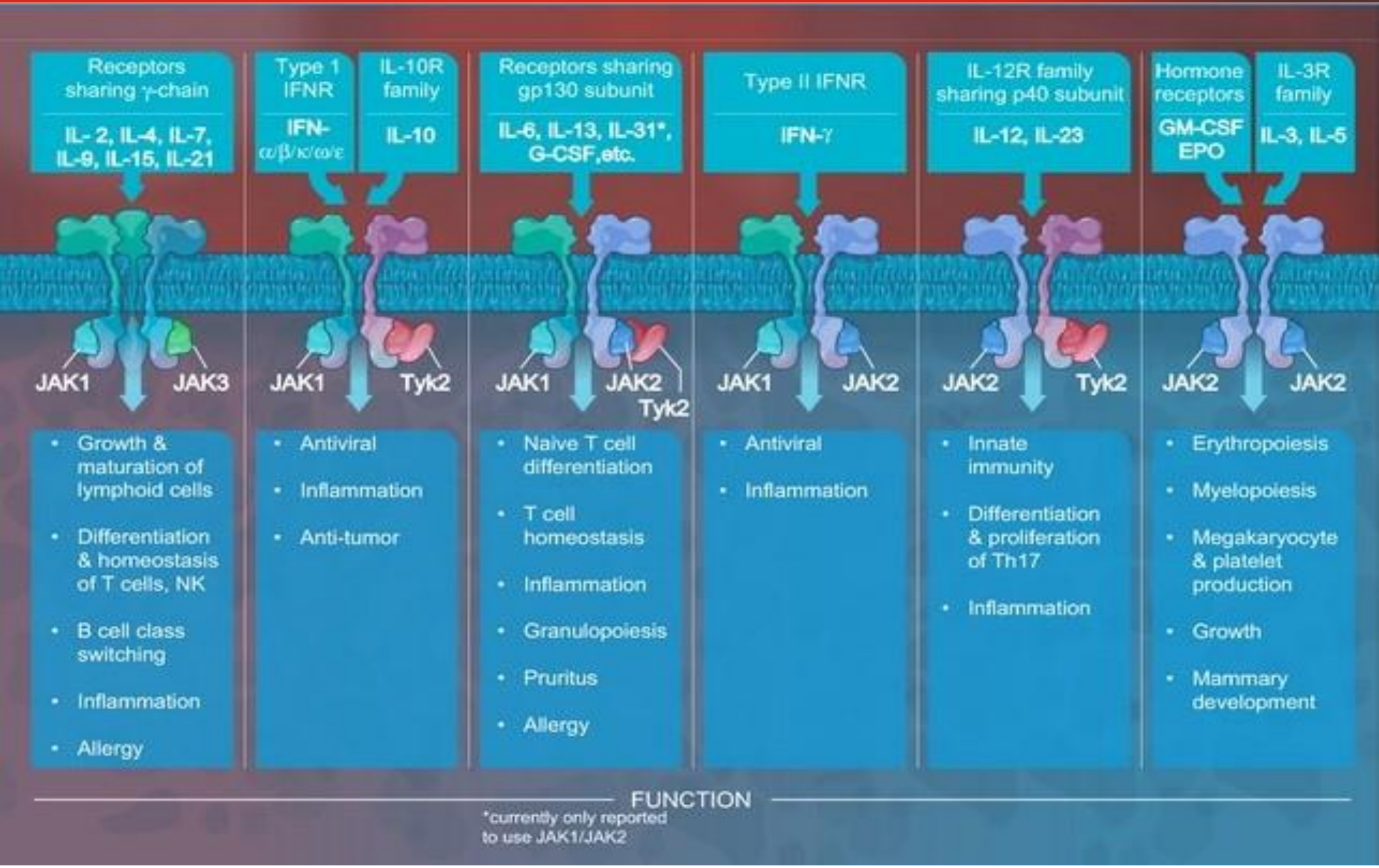


JAK Inhibition: Backdoor to the Heart?

Dr EUGENE LIM
Rheumatologist
ELIM Rheumatic Centre
MBBS (Singapore), MMed (Int Med), FAMS (Rheum), FACR (USA), RhMSUS (ACR), RMSK (APCA), CIPS (WIP)

Lilly

Cytokines Signalling Through JAK Heterodimers



JAK Inhibitors Phase 3 Trials

Trial (JAKi)	ORAL (Tofacitinib)	RA (Baricitinib)	SELECT (Upadacitinib)	FINCH (Filgotinib)	RAJ (Peficitinib)
csDMARD naïve	Start	Begin	Early	3	
csDMARD IR	Scan (MTX) Sync	Build	Next	1	4
MonoJAK	Solo Strategy		Monotherapy		
bDMARD IR	Step	Beacon	Beyond	2	
***vs* bDMARD**	Standard Strategy	Beam	Choice (ABA) Compare (ADA)		3 (ETA)
LTE	Sequel (9.5yrs)	Beyond (6yrs)		4	NCT01638013
Tapering	Swift (MTX)	Beyond (dose)			

The Background

Lilly

Incident Myocardial Infarction Associated with Major Types of Arthritis in the General Population

O Schier *et al*. Ann Rheum Dis 2017; 76:1396-1404

Methodology & Results

- Systematic review and meta-analysis of published data

Disease	RR	95% CI
RA	1.69	1.50-1.90
Gout	1.47	1.24-1.73
PsA	1.41	1.17-1.69
OA	1.31	1.01-1.71
AS	1.24	0.93-1.65 (ns)

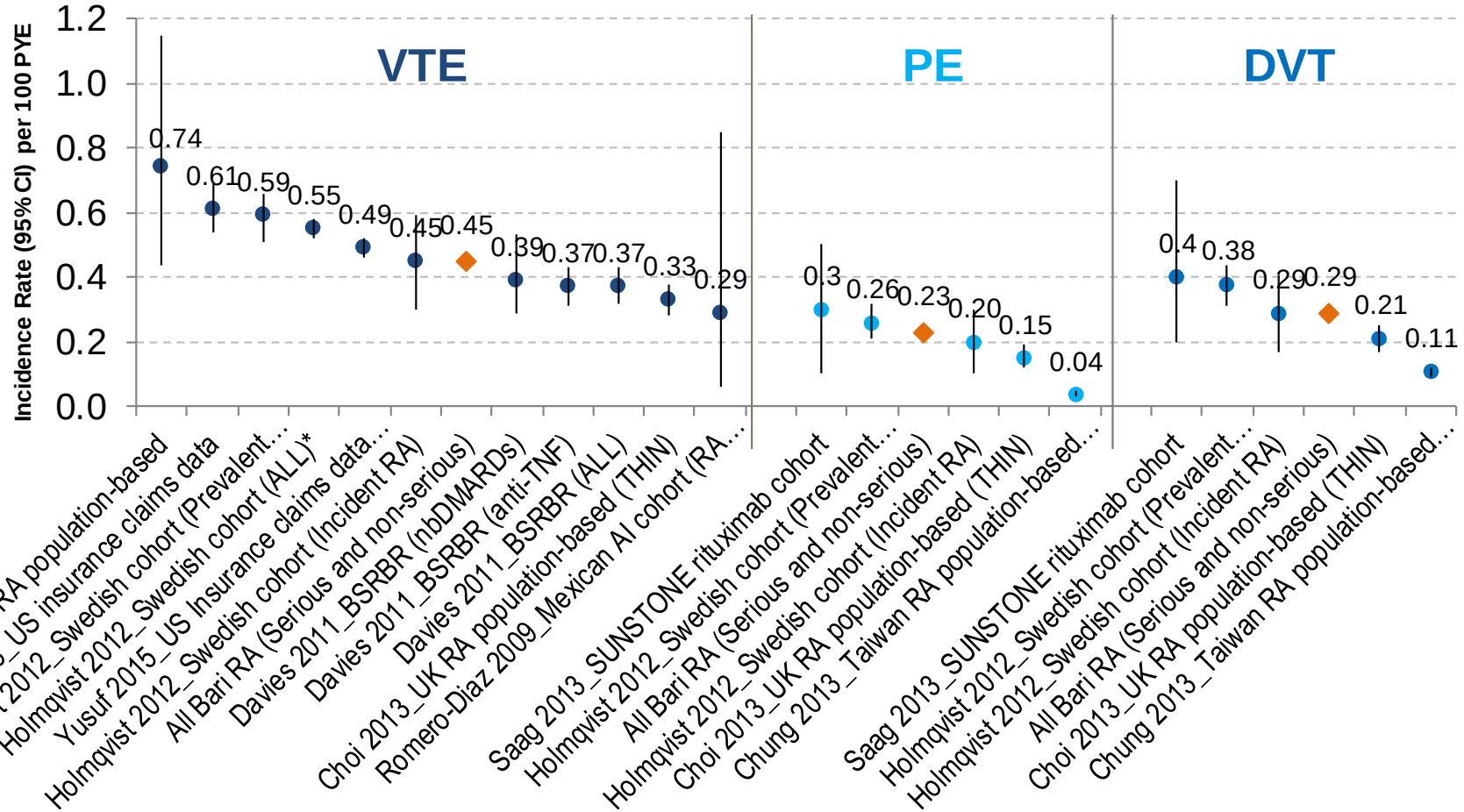
Venous Thromboembolism Risk in Patients with RA

RR 1.6-2.4

- ME Holmqvist *et al*. JAMA 2012; 308:1350-1356
- SC Kim *et al*. Arthritis Care Res 2013; 65:1600-1607
- JJ Lee *et al*. Arthritis Res Therapy 2014; 16:435

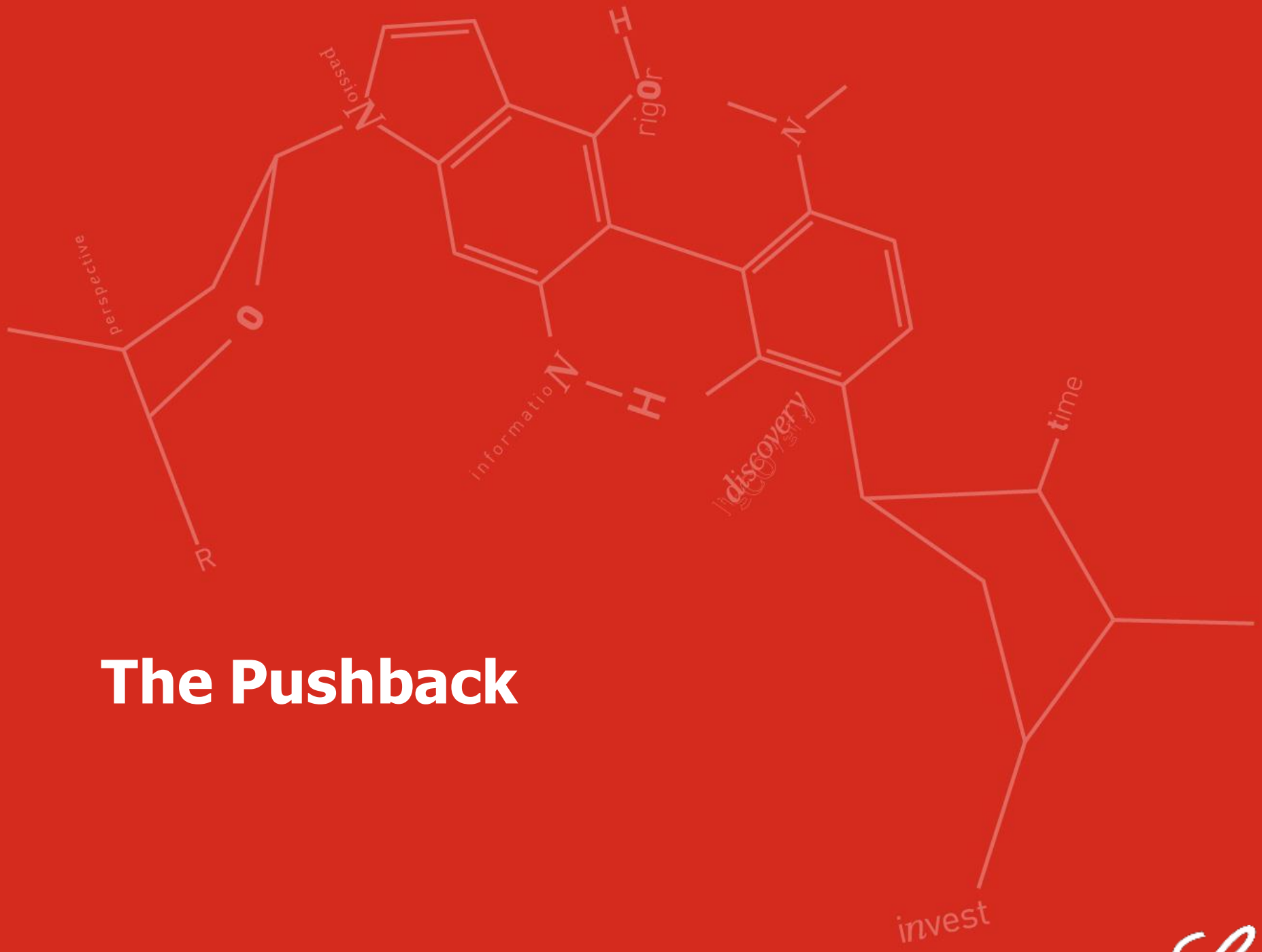
VTE Incidence Rates

In Observational Studies and in All BARI RA[a]



IR 0.29-0.79 /100PY

[a]All BARI RA, data as of Sep 1 2016.
Data on file, Eli Lilly and Company



The Pushback

Lilly

Cardiovascular Safety during Treatment with Baricitinib in Rheumatoid Arthritis

M Weinblatt *et al*. Arthritis Rheumatol 2017 Sep; 69(suppl 10):2352

Methodology

- 8 completed (4 x phase 3: Build, Beacon, Beam, Begin) and 1 ongoing LTE (Beyond) Baricitinib in RA trials
- 3,492 patients, 6,637 patient-years up till 1 Sep 2016
- Placebo comparison up to 24 weeks from 6 studies

Results

n (IR/100 pt-yr)	Baricitinib 4mg	Placebo
MACE	3 (0.8)	2 (0.5)
DVT	3 (0.7)	0 (0)
PE	3 (0.7)	0 (0)

- No difference in MACE
- Imbalance of Deep Vein Thrombosis and Pulmonary Embolism (Venous Thromboembolism) in Baricitinib 4mg group
- All 6 VTEs occurred in high-risk group: >60yo, high BMI (5/6 >35), COX2i use, previous thrombosis

SELECT Next: Safety and Efficacy of Upadacitinib in Patients with RA and Inadequate Response to Conventional Synthetic DMARDs

GR Burmester *et al.* Lancet 2018 Jun; 391(10139):2503-2512

Methodology

- Multi-centre double-blind randomised controlled phase 3 trial
- 661 patients randomized to 30mg, 15mg and placebo for **first 12 weeks**, with placebo group randomized to active groups in **next 12 weeks**

Results

Efficacy at 12 wks	30mg	15mg	PBO	*p*
ACR20	66.2%	63.8%	35.7%	<0.001
DAS28-CRP <3.2	47.9%	48.4%	17.2%	<0.001
HAQ-DI	-0.54	-0.59	-0.25	<0.001

- No VTE or deaths
- 3 x MACE in active groups
- 2 x malignancies in active groups
- 30mg group had higher incidence of Herpes Zoster and serious infections

SELECT Beyond: Safety and Efficacy of Upadacitinib in Patients with Active Rheumatoid Arthritis Refractory to Biologic DMARDs

MC Genovese *et al*. Lancet 2018 Jun; 391(10139):2513-2524

Results

Efficacy at 12 wks	30mg	15mg	PBO	*p*
ACR20	56%	65%	28%	<0.001
DAS28-CRP <3.2	42%	43%	14%	<0.001
HAQ-DI	-0.42	-0.39	-0.17	<0.001

AEs at 24 wks	30mg	15mg	All Doses	PBO (0-12 wks)
PE	1	3	4	0
DVT	0	1	1	0
MACE	1	3	4	0
CA (exc NMSC)	2	2	4	0
Herpes Zoster	7	3	10	1
Serious Infection	7	4	11	0
Death	1 (CF/PE)	1 (?)	2	0

Analysis of Spontaneous Post-Market Case Reports Submitted to the FDA Regarding Thromboembolic Adverse Events and JAK Inhibitors

A Verden *et al*. Drug Safety 2018 Apr; 41(4):357-361

Methodology

- FDA Adverse Event Reporting System (FAERS) database
- Reporting Odds Ratio (ROR) and Empirical Bayesian Geometric Mean (EBGM)
- Detect AEs with higher than expected reporting rates compared to other drugs

Results

- Increased pulmonary thrombosis reported for Tofacitinib, Tofacitinib XR & Ruxolitinib
- Increased Portal Vein Thrombosis for Ruxolitinib

JAKi	*n* (ROR/EBGM)	PT	PE	PVT	DVT
Ruxolitinib	190	9 (1.46/1.25)	55	11 (4.08/3.04)	40
Tofacitinib	115	16 (2.46/2.46)	36	0	18
Tofacitinib XR	12	3 (2.48/1.56)	3	0	1

Limitations

- No denominator and duration, so Incidence Rates cannot be calculated
- Reporting is voluntary
- Disease activity (refractory inflammation) and prothrombotic comorbidities (myeloproliferative disorders) not accounted for
- Lumping JAKi's with different selectivities as a class

A3921133: Safety Study of Tofacitinib vs TNF Inhibitors in Subjects with Rheumatoid Arthritis

Pfizer Press Release

Methodology

- Post-marketing study in RA required of Pfizer by FDA, ongoing till end 2019

Results

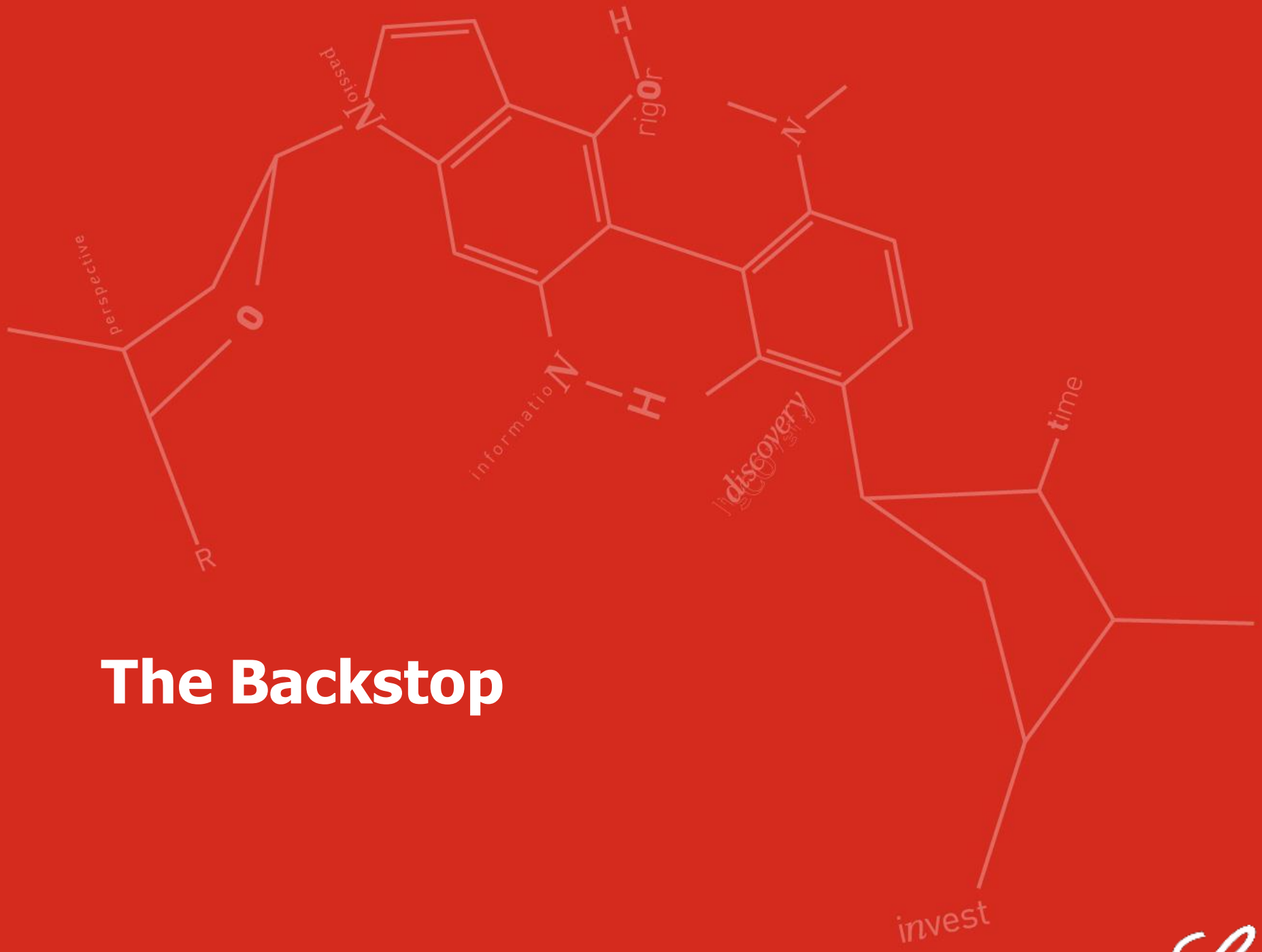
- Imbalance in pulmonary thrombosis and deaths found only in >/= 50yo with >/= 1 CV risk factor taking Tofacitinib 10mg *bd*

Treatment	Patient-Years	Pulmonary Thrombosis	Deaths
Tofa 10mg *bd*	3884	19	45
TNFi	3982	3	25

Timeline & Recommendations

- Findings released by FDA in Feb 2019
- **Black box** warning in July 2019 on increased risk of clots and death in RA treated with Tofa 10mg *bd*
- Tofa 10mg *bd* not approved in RA reiterated
- Tofa 10mg *bd* in UC only after TNFi inadequate response or intolerance, tapering to 5mg *bd* for maintenance

https://investors.pfizer.com/investor-news/press-release-details/2019/Pfizer-Announces-Modification-to-Ongoing-Tofacitnib-FDA-Post-Marketing-Requirement-Study-in-Patients-with-Rheumatoid-Arthritis/default.aspx



The Backstop

Lilly

Thromboembolism with JAK Inhibitors for Rheumatoid Arthritis: How Real is the Risk?

IC Scott *et al*. Drug Safety 2018 Jul; 41(7):645-653

Methodology & Results

- Based on all public trial data

Patient Group	TE IR (/100 pt-yrs)
Non-RA	0.1-0.4
RA	0.3-0.7
RA on csDMARD	0.4-0.8
RA on Baricitinib	0.5

Limitations

- Trial subjects not representative of general RA population (less comorbidities, low TE risk)
- Short duration & small numbers (not powered to detect AEs)

Conclusions

- RA patients are at higher risk compared to the healthy population for developing thromboembolic events, independent of treatment with csDMARDs or with Baricitinib
- Large registry data and long-term extension observational studies are required to better quantify the real TE risk with JAKi for RA

Incidence of Thromboembolic Events in the Tofacitinib RA, Psoriasis, Psoriatic Arthritis and Ulcerative Colitis Development Programmes

PJ Mease *et al*. Ann Rheum Dis 2018 Jun; 77:983

Methodology

- All Tofacitinib clinical trials and CORRONA registry database (> 100,000 patient-years on csDMARDs, biologics, Tofacitinib)

Results

	Placebo-controlled cohort[a]			Dose-comparison cohort[b]			
n/N IR (95% CI)	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Placebo	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	Adalimumab 40 mg SC Q2W	Methotrexate 20 mg QW
Rheumatoid arthritis (N=5368; PY=4440)							
DVT	0/1849 0.0 (0.0, 0.9)	0/2024 0.0 (0.0, 0.8)	1/1079 0.4 (0.0, 2.4)	1/1849 0.1 (0.0, 0.3)	1/2024 0.1 (0.0, 0.3)	0/257 0.0 (0.0, 1.9)	2/223 0.7 (0.1, 2.5)
PE	0/1849 0.0 (0.0, 0.9)	0/2024 0.0 (0.0, 0.8)	1/1079 0.4 (0.0, 2.4)	2/1849 0.1 (0.0, 0.4)	3/2024 0.2 (0.0, 0.4)	0/257 0.0 (0.0, 1.9)	0/223 0.0 (0.0, 1.3)
Psoriasis (N=3662; PY=8763)[c]							
DVT	0/1123 0.0 (0.0, 1.0)	0/1120 0.0 (0.0, 1.0)	0/530 0.0 (0.0, 2.1)	0/1217 0.0 (0.0, 0.4)	0/1219 0.0 (0.0, 0.4)	–	–
PE	0/1123 0.0 (0.0, 1.0)	0/1120 0.0 (0.0, 1.0)	0/530 0.0 (0.0, 2.1)	0/1217 0.0 (0.0, 0.4)	0/1219 0.0 (0.0, 0.4)	–	–
Psoriatic arthritis (N=783; PY=791)[c]							
DVT	0/238 0.0 (0.0, 6.8)	0/236 0.0 (0.0, 6.8)	0/236 0.0 (0.0, 6.9)	0/347 0.0 (0.0, 1.8)	1/344 0.5 (0.0, 2.8)	0/106 0.0 (0.0, 4.0)	–
PE	0/238 0.0 (0.0, 6.8)	0/236 0.0 (0.0, 6.8)	0/236 0.0 (0.0, 6.9)	0/347 0.0 (0.0, 1.8)	0/344 0.0 (0.0, 1.9)	0/106 0.0 (0.0, 4.0)	–
Ulcerative colitis (N=1156; PY [DVT] =1420; PY [PE]=1418)							
DVT	N/A	0/938 0.0 (0.0, 2.2)	1/282 2.0 (0.1, 11.0)	0/198 0.0 (0.0, 2.5)	0/196 0.0 (0.0, 2.4)	–	–
PE	N/A	0/938 0.0 (0.0, 2.2)	1/282 2.0 (0.1, 11.0)	0/198 0.0 (0.0, 2.5)	0/196 0.0 (2.4)	–	–

- No imbalance of DVT/PE risk in Tofacitinib patients

ORAL Sequel: Safety and Efficacy of Tofacitinib for up to 9.5 years in the Treatment of RA

J Wollenhaupt *et al*. Arthritis Res & Therapy 2019 Apr; 21:89

Methodology

- Global open-label long-term extension study: 4481 patients 16,291 patient-years

Results

IR (/100pt-yr)	5mg *bd*	10mg *bd*	All Doses
MACE	0.5	0.4	0.4
PE	0.1	0.1	0.1
DVT	0.1	0.1	0.1
Herpes Zoster	2.3	3.7	3.4
Serious Infections	1.9	2.6	2.4
Cancers (exc NMSC)	0.8	0.8	0.8
All-Cause Mortality	0.3	0.3	0.3

Conclusions

- No imbalance of risk for MACE/PE/DVT between Tofacitinib 5mg *bd* and 10mg *bd*
- Higher IR of Herpes Zoster and serious infections in Tofacitinib 10mg *bd* group

Impact of JAK Inhibitors on Risk of Cardiovascular Events in Patients with Rheumatoid Arthritis

W Xie *et al*. Ann Rheum Dis 2019 Aug; 78:1048-1054

Methodology

- Systematic review and meta-analysis of 26 RCTs randomising 11,799 patients

Results

OR (95% CI)	CVE	MACE	VTE
All JAKi	1.04 (0.61-1.76)	0.80 (0.36-1.75)	1.16 (0.48-2.81)
Tofacitinib (5mg *vs* 10mg)	0.63 (0.26-1.54)		
Baricitinib (2mg *vs* 4mg)	1.21* (0.51-2.83)		
Upadacitinib (15mg *vs* 30mg)	3.29 (0.59-18.44)		
Peficitinib	0.43 (0.07-2.54)		

- No dose-dependent risk difference except:

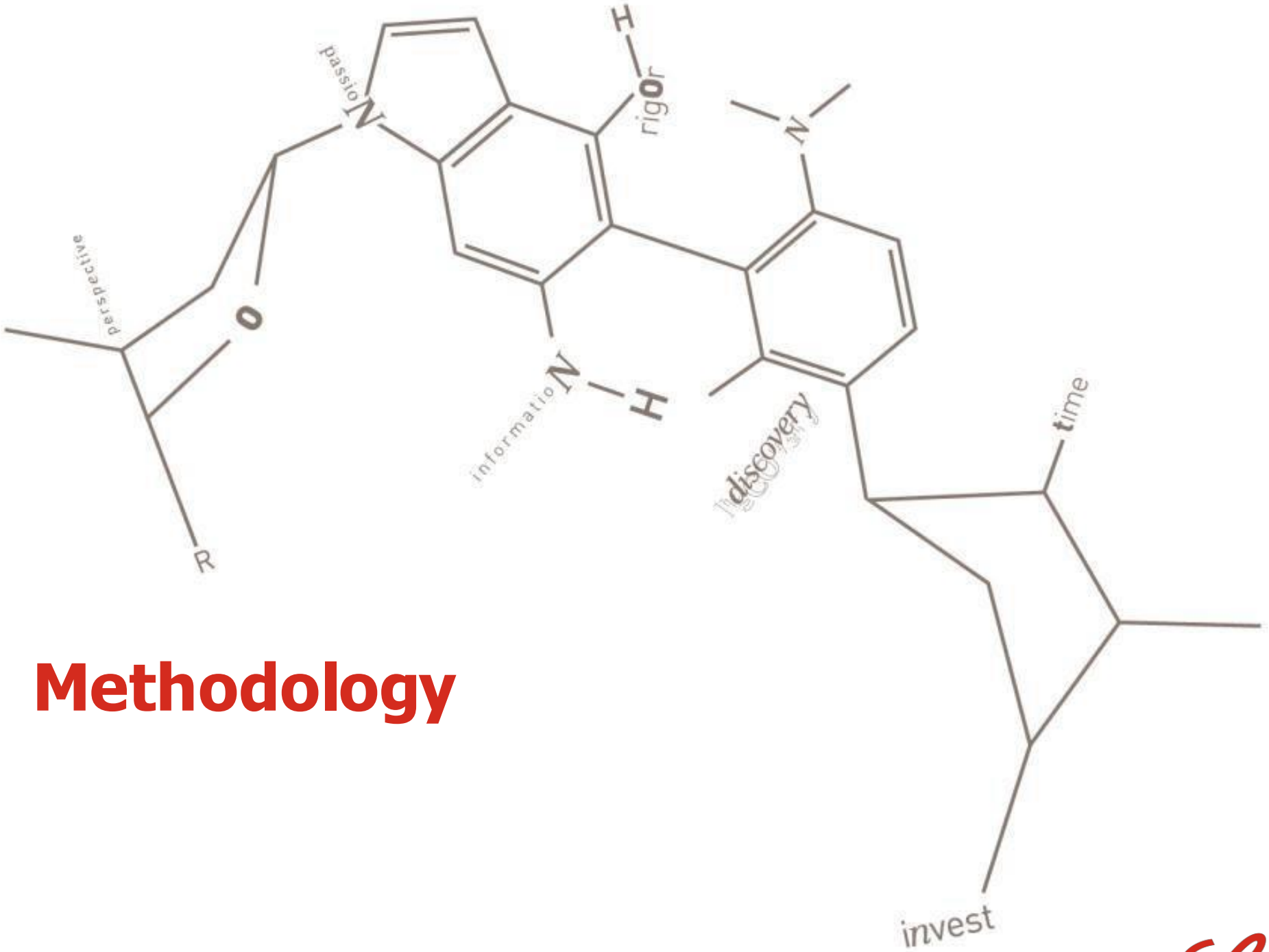
*Baricitinib 2mg *vs* 4mg = 0.19 (CI 0.04-0.88, $p = 0.03$)

Cardiovascular Safety During Treatment with Baricitinib in Rheumatoid Arthritis

Peter C. Taylor, Michael E. Weinblatt, Gerd R. Burmester, Terence P. Rooney, Sarah Witt, Chad D. Walls, Maher Issa, Claudia A. Salinas, Chadi Saifan, Xin Zhang, Anabela Cardoso, Miguel A. González-Gay, Tsutomu Takeuchi

Arthritis Rheumatol. 2019 Jan 21. doi: 10.1002/art.40841. [Epub ahead of print]

Lilly



Methodology

Integrated safety analysis datasets

Disclaimer: Indication of Baricitinib - 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.

Integrated analysis set	Trials[1-3]							Treatment period
	Phase 1 JADB	Phase 2 JADA JADC JADN[a]	Phase 3					
			RA BEGIN	RA BEAM	RA BUILD	RA BEACON	RA BEYOND	
6-study BARI 4-mg RA PC (N=2067)		JADA✓ JADN✓ JADC✓		✓	✓	✓		0-24 Weeks[b]
Ext. BARI 2-mg vs. 4-mg RA (N=958)		JADA✓ JADN✓ JADC×			✓	✓	✓	All BARI 2-mg or 4-mg exposure up to data-cut[c]
ALL BARI RA (N=3492)	✓	JADA✓ JADN✓ JADC✓	✓	✓	✓	✓	✓	All BARI exposure up to data-cut

Note: All patients were taking csDMARD(s) as background therapy per-protocol, except for patients in Phase 3 RA-BEGIN where MTX was study drug for patients randomized to either the MTX monotherapy or BARI 4-mg+MTX arms, and where BARI monotherapy patients had no background csDMARDs or MTX; N numbers are combined values from each treatment arm; [a]Phase 2 studies had a 12-week PC period; [b]Patient data included in analysis set until rescue, if it occurs (possible from Week 16 [Phase 3]) or end of the PC period for patients receiving placebo (Phase 2, Week 12); [c]Patient data included in analysis set until rescue if it occurs (possible from Week 16 [Phase 3]) or dose change (including dose-taper in RA-BEYOND)

csDMARD=conventional synthetic disease-modifying antirheumatic drug; Ext.=extended; PC=placebo-controlled; RA=rheumatoid arthritis

1. Data on file, Eli Lilly and Company; 2. Taylor PC et al. *N Engl J Med* 2017;376(7):652-62; 3. Genovese M et al. Presented at ACR 2018. Abstract 962

Exposure summary: Integrated datasets

BARI BARICITINIB 19 MU
April 1, 2017

	BARI RA PC, Weeks 0-24[1]			Ext. BARI 2-mg vs. 4-mg RA[2]		All BARI RA[1,2]		
	PBO	BARI 2-mg	BARI 4-mg	BARI 2-mg	BARI 4-mg	BARI 2-mg[a]	BARI 4-mg[a]	All BARI[b]
Patients treated (N)	1070	479	997	479	479	1005	3107	3492
PYE[c]	393.8	185.8	409.4	604.9	645.9	1274.6	6391.6	7860.3

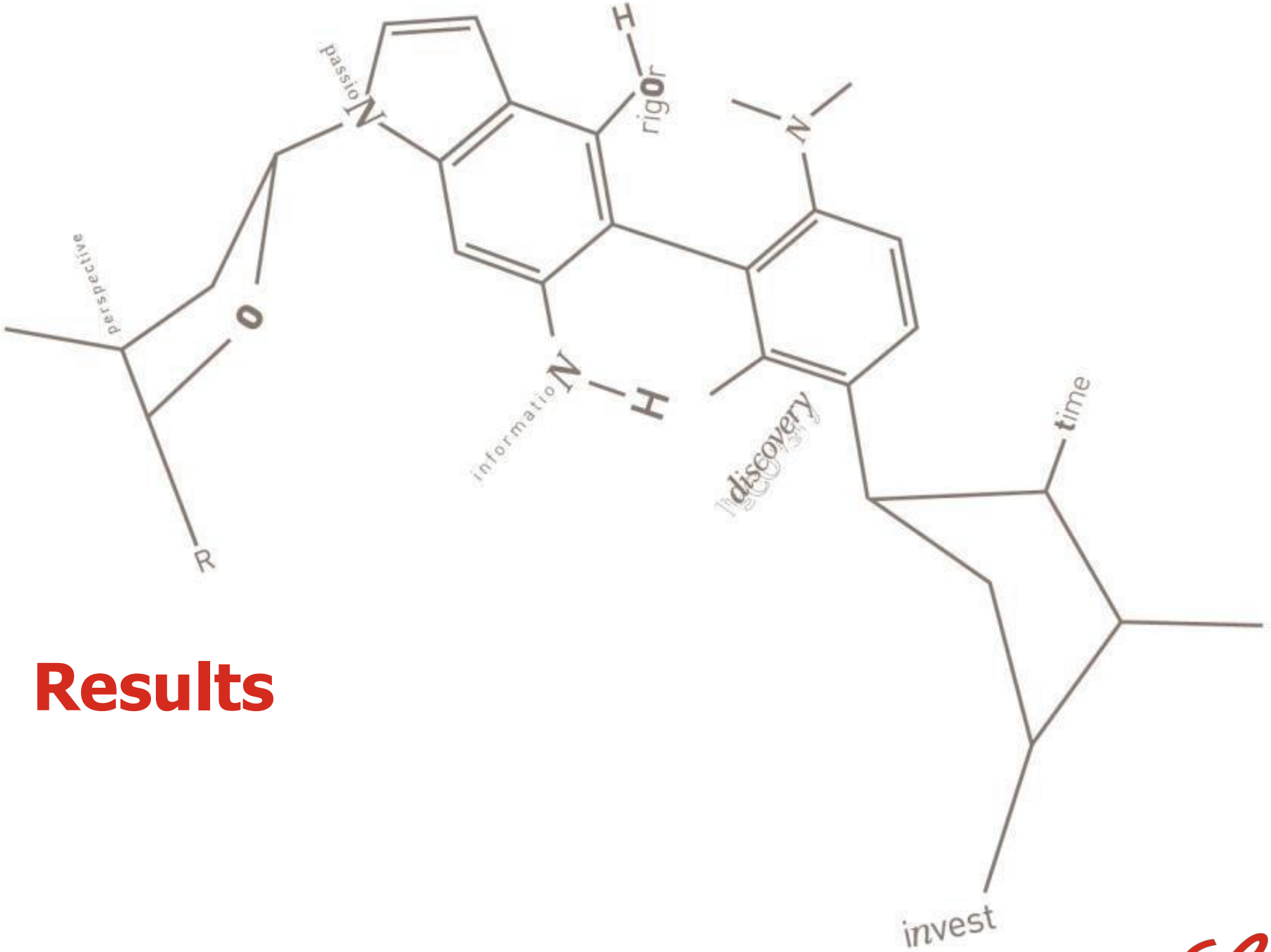
[a]All BARI RA, Phases 2-3, cumulative exposure; [b]All BARI RA, Phases 1-3

Ext.=extended; MU=month update; PC=placebo-controlled; PYE=patient years of exposure; RA=rheumatoid arthritis

1. Data on file, Eli Lilly and Company; 2. Genovese M et al. Presented at ACR 2018. Abstract 962

Evaluation of events

- In Phase 3 trials, potential **MACE and other CV events** (hospitalization for unstable angina, hospitalization for heart failure, serious arrhythmia, resuscitated sudden death, cardiogenic shock, or coronary revascularizations) were adjudicated by an independent, external Clinical Endpoint Committee
- **ATE** comprised of MI and ischemic stroke, plus Medical Dictionary for Regulatory Activities (MedDRA) preferred terms indicative of other acute ATE; where available (Phase 3 for applicable event types), adjudicated data were used
- **DVT and PE** were not independently adjudicated. Review was conducted by sponsor medical staff to identify reported events of DVT and PE using a standardized MedDRA query (SMQ) from the Embolic and Thrombotic Events SMQ, including all sub-SMQs in addition to MedDRA preferred terms of "deep vein thrombosis" and "pulmonary embolism"
- For **CHF**, signal detection analysis was conducted using the broad and narrow terms of the Cardiac Failure SMQ


passio
rigor
perspective
informatio
discovery
time
invest
R

Results

MACE, ATE and DVT/PE overview

BARI BARICITINIB 19 MU
April 1, 2017

Safety measure	BARI RA PC Weeks 0-24			Ext. BARI 2-mg vs. 4-mg RA		All BARI RA
	PBO (N=1070)	BARI 2-mg (N=479)	BARI 4-mg (N=997)	BARI 2-mg (N=479)	BARI 4-mg (N=479)	All BARI (N=3492)
MACE[1]	2 (0.5)	0	3 (0.8)	1 (0.2)	2 (0.4)	38 (0.5)
MI[2]	1 (0.3)	0	1 (0.3)	1 (0.2)	1 (0.2)	17 (0.2)
CV death[2]	1 (0.3)	0	2 (0.5)	0	1 (0.2)	11 (0.2)
Stroke[2]	1 (0.3)	0	1 (0.3)	0	1 (0.2)	15 (0.2)
ATE[1]	2 (0.5)	2 (1.0)	2 (0.5)	3 (0.5)	3 (0.5)	35 (0.4)
DVT/PE[1]	0	0	6 (1.4)	3 (0.5)	4 (0.6)	42 (0.5)
DVT[2]	0	0	3 (0.7)	3 (0.5)	2 (0.3)	30 (0.4)
PE[2]	0	0	3 (0.7)	1 (0.2)	2 (0.3)	19 (0.2)

Data presented are n (IR)

ATE=arterial thrombotic events; CV=cardiovascular; DVT=deep vein thrombosis; Ext.=extended; IR=incidence rate; MACE=major adverse cardiovascular event; MI=myocardial infarction; MU=month update; PC=placebo-controlled; PE=pulmonary embolism; RA=rheumatoid arthritis; 1. Weinblatt M et al. Presented at ACR 2018; 2. Data on file, Eli Lilly and Company

Congestive heart failure (CHF)

	Pbo	Bari 2	Bari 4	Extended Bari 2	Extended Bari 4	Extended All Bari
CHF[f] TEAE, n [EAIR]						
Broad Terms	17 [4.3]	7 [3.8]	10 [2.4]	14 [2.3]	19 [2.9]	128 [1.6]
Narrow Terms	1 [0.3]	-	1 [0.2]	3 [0.5]	1 [0.2]	19 [0.2]
CHF[f] SAE, n [EAIR]						
Broad Terms	0	0	1 [0.2]	1 [0.2]	2 [0.3]	11 [0.1]
Narrow Terms	0	0	1 [0.2]	1 [0.2]	2 [0.3]	10 [0.1]

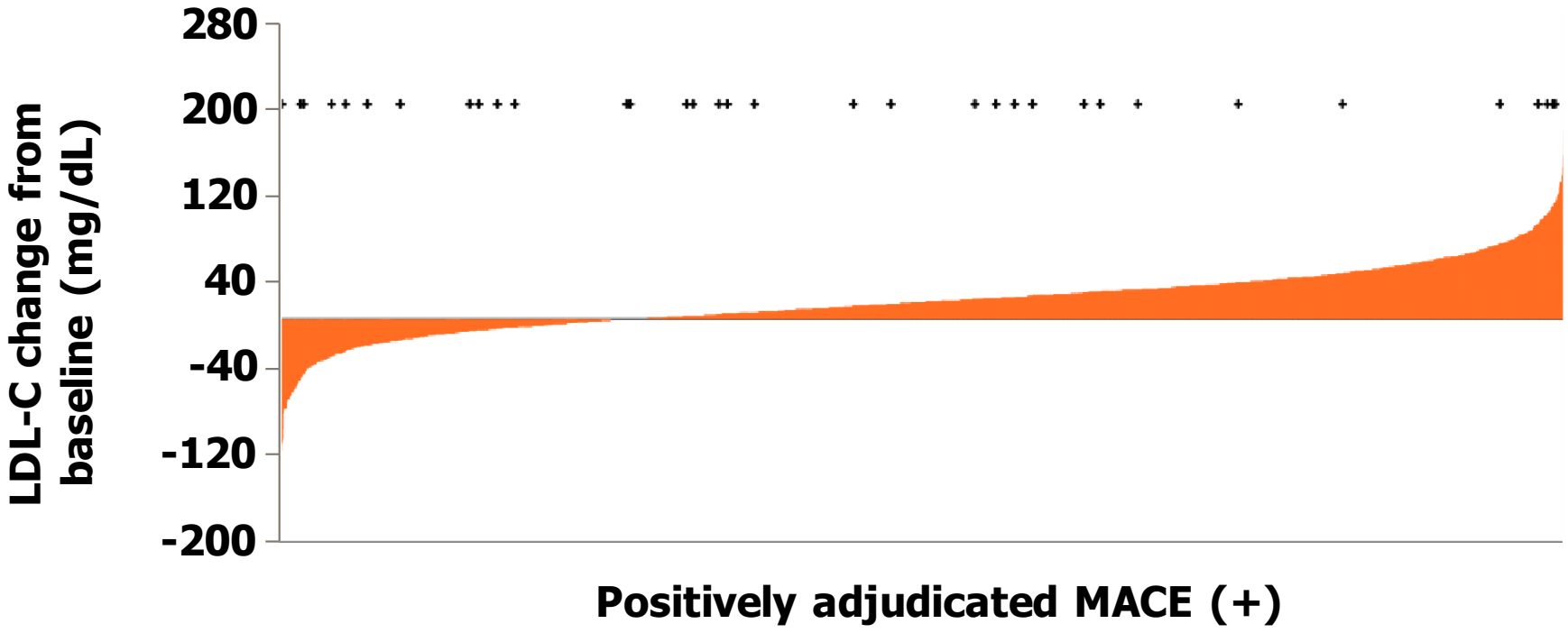
- Reported CHF was similar between placebo and baricitinib, with few SAEs

MACE and change in LDL-C: All BARI RA

BARI BARICITINIB 19 MU
April 1, 2017

No observed pattern that LDL-C changes are associated with MACE

MACE against LDL-C change from baseline in All BARI RA[a]



[a]Studies with applicable data: RA-BEGIN, RA-BEAM, RA-BEACON, RA-BUILD, and RA-BEYOND

LDL-C=low-density lipoprotein-cholesterol; MACE=major adverse cardiovascular event; MU=month update; RA=rheumatoid arthritis

Data on file, Eli Lilly and Company

MACE, ATE and DVT/PE overview

BARI BARICITINIB 19 MU
April 1, 2017

Safety measure	BARI RA PC Weeks 0-24			Ext. BARI 2-mg vs. 4-mg RA		All BARI RA
	PBO (N=1070)	BARI 2-mg (N=479)	BARI 4-mg (N=997)	BARI 2-mg (N=479)	BARI 4-mg (N=479)	All BARI (N=3492)
MACE[1]	2 (0.5)	0	3 (0.8)	1 (0.2)	2 (0.4)	38 (0.5)
MI[2]	1 (0.3)	0	1 (0.3)	1 (0.2)	1 (0.2)	17 (0.2)
CV death[2]	1 (0.3)	0	2 (0.5)	0	1 (0.2)	11 (0.2)
Stroke[2]	1 (0.3)	0	1 (0.3)	0	1 (0.2)	15 (0.2)
ATE[1]	2 (0.5)	2 (1.0)	2 (0.5)	3 (0.5)	3 (0.5)	35 (0.4)
DVT/PE[1]	0	0	6 (1.4)	3 (0.5)	4 (0.6)	42 (0.5)
DVT[2]	0	0	3 (0.7)	3 (0.5)	2 (0.3)	30 (0.4)
PE[2]	0	0	3 (0.7)	1 (0.2)	2 (0.3)	19 (0.2)

Data presented are n (IR)

ATE=arterial thrombotic events; CV=cardiovascular; DVT=deep vein thrombosis; Ext.=extended; IR=incidence rate; MACE=major adverse cardiovascular event; MI=myocardial infarction; MU=month update; PC=placebo-controlled; PE=pulmonary embolism; RA=rheumatoid arthritis; 1. Weinblatt M et al. Presented at ACR 2018; 2. Data on file, Eli Lilly and Company

DVT/PE events occurred in BARI patients in the randomized controlled periods in 2 of the 8 completed BARI RA studies

Disclaimer: Indication of Baricitinib - 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.

Study	PBO	1-mg	2-mg	4-mg	7-mg	8-mg	10-mg	MTX mono	ADA
Phase 2 RA studies									
JADC (N=125)	0	–	–	0	0	–	0	–	–
JADA (N=300)	0	0	0	0	–	0	–	–	–
JADN (N=145)	0	0	0	0	–	0	–	–	–
Phase 3 RA studies									
RA-BEGIN (N=584)	–	–	–	0	–	–	–	1[a]	–
RA-BEAM (N=1305)	0	–	–	4	–	–	–	–	0
RA-BUILD (N=684)	0	–	0	2	–	–	–	–	–
RA-BEACON (N=527)	0	–	0	0	–	–	–	–	–
RA-BALANCE (N=290)	0	–	–	0	–	–	–	–	–

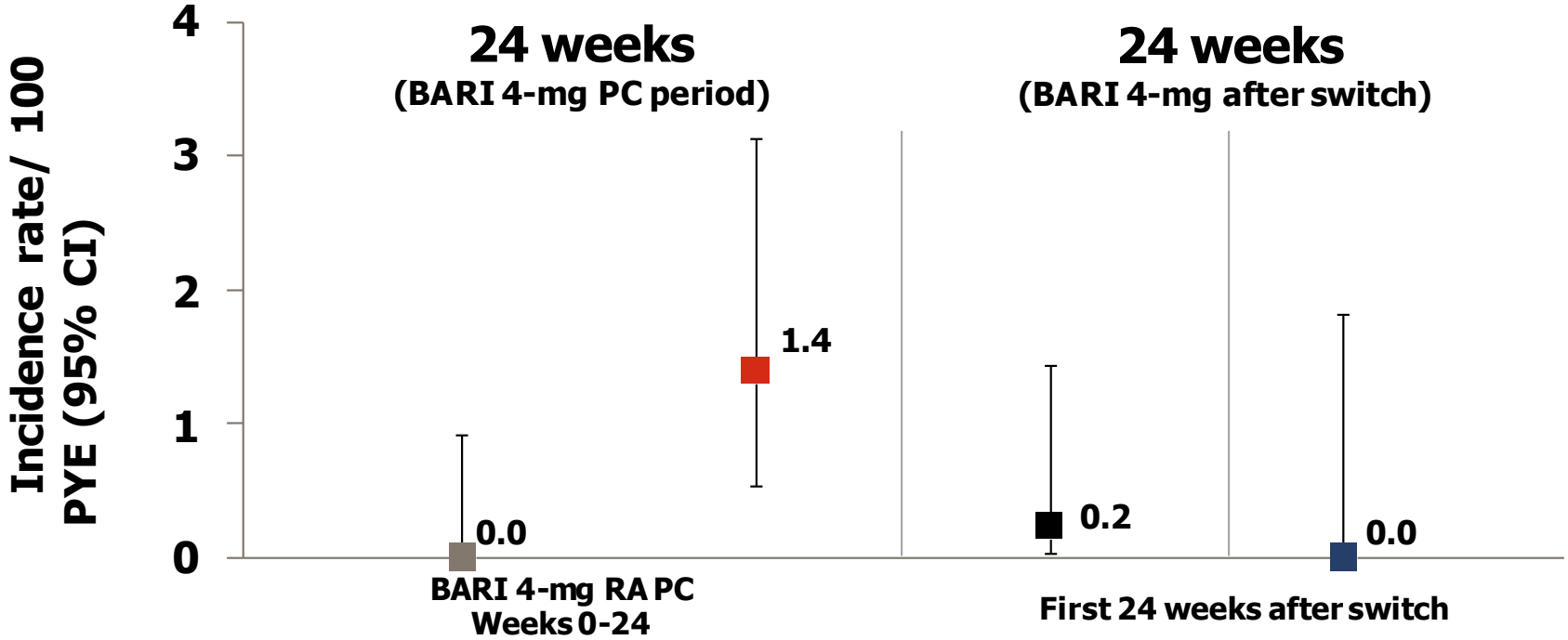
[a]PE (fatal)

Data include post-treatment follow-up where available; DVT=deep vein thrombosis; PE=pulmonary embolism; RA=rheumatoid arthritis

1. Data on file, Eli Lilly and Company; 2. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf

DVT/PE incidence rates after switch from placebo or active comparator to baricitinib

One patient (among 928 patients) reported a DVT/PE event during 24 weeks of treatment with BARI 4-mg following switch from placebo and no patients reported an event during 24 weeks following switch from an active comparator



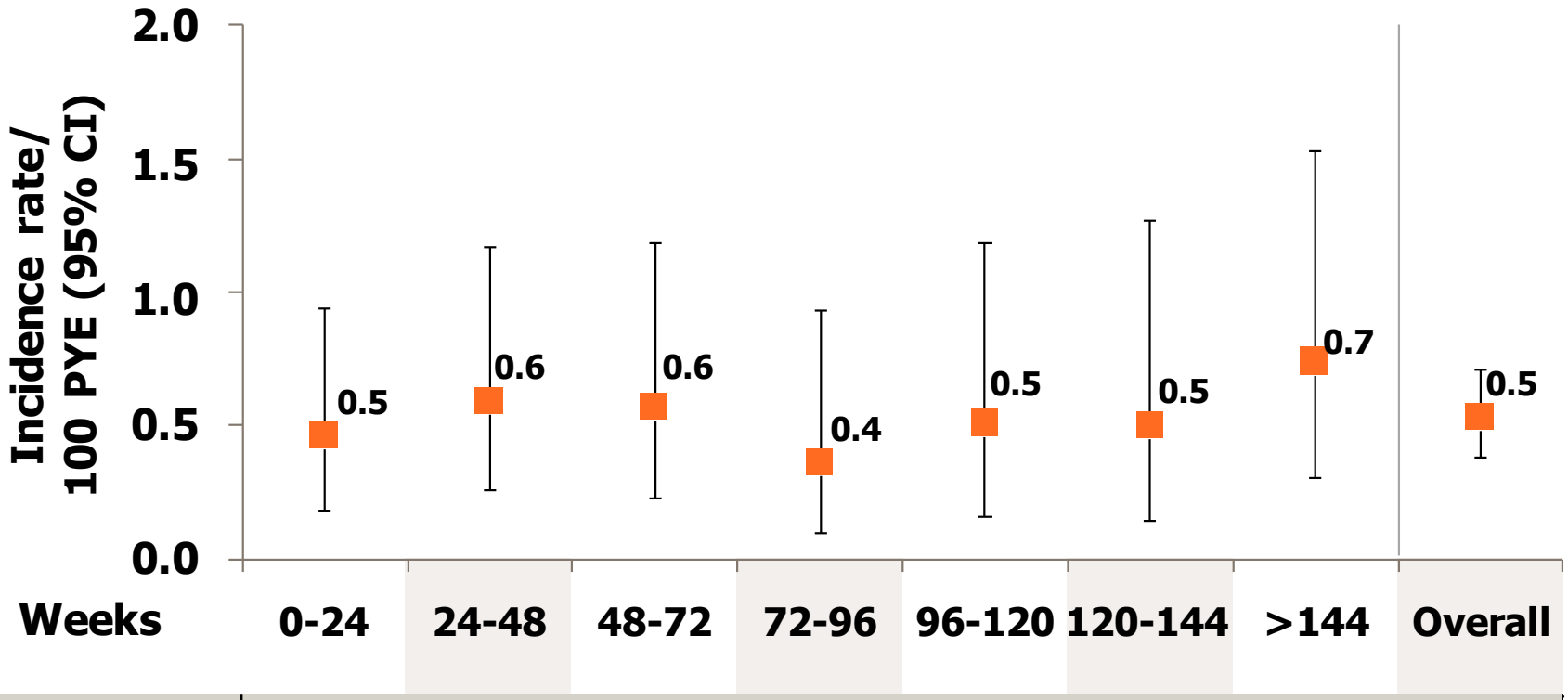
	PBO	BARI 4-mg	PBO → BARI 4-mg	Active comparator[a] → BARI 4-mg
All patients	1070	997	928	451
With events	0	6	1	0
PYE	405.8	418.1	409.5	203.0

Note: PYE=PYR (patient years at risk), where exposure is censored at the time of event; [a]ADA+MTX; DVT=deep vein thrombosis; PC=placebo-controlled; PE=pulmonary embolism; PYE=patient years of exposure; PYR=patient years at risk; RA=rheumatoid arthritis; Weinblatt M et al. Presented at ACR 2018. Abstract 2815

DVT/PE over time: All BARI RA

BARI BARICITINIB 19 MU
April 1, 2017

Rates of DVT/PE remained stable over time



All patients	3492	3158	2814	2500	2266	1982	1486	3492
With events	7	8	7	4	5	4	7	42
PYE	1533.4	1348.9	1227.3	1101.9	985.9	806.0	945.1	7948.6

Note: PYE=PYR (patient years at risk), where exposure is censored at the time of event; DVT=deep vein thrombosis; MU=month update; PE=pulmonary embolism; PYE=patient years of exposure; PYR=patient years at risk; RA=rheumatoid arthritis; Weinblatt M et al. Presented at ACR 2018. Abstract 2815

Disposition and clinical management of patients with DVT/PE: All BARI RA

BARI BARICITINIB 19 MU
April 1, 2017

	Treatment-emergent adverse event	Serious adverse event
DVT/PE event, n (IR)[a]	42 (0.5)	28 (0.4)
DVT event, n (IR)[a]	30 (0.4)	17 (0.2)
PE event, n (IR)[a]	19 (0.2)	17 (0.2)

42 patients with reported DVT/PE

3450 patients without DVT/PE

Time to event from first dose of BARI ranged from **37 to 1658 days**

28 **Patients exposed to BARI post-DVT/PE**

With continuous anticoagulation	25
Without continuous anticoagulation	3

2 of 28 had a recurrence, 1 and 2 years after first event[b]

12 **Patients reported DVT/PE after BARI discontinuation**

10 **Temporary interruptions of BARI due to DVT/PE**

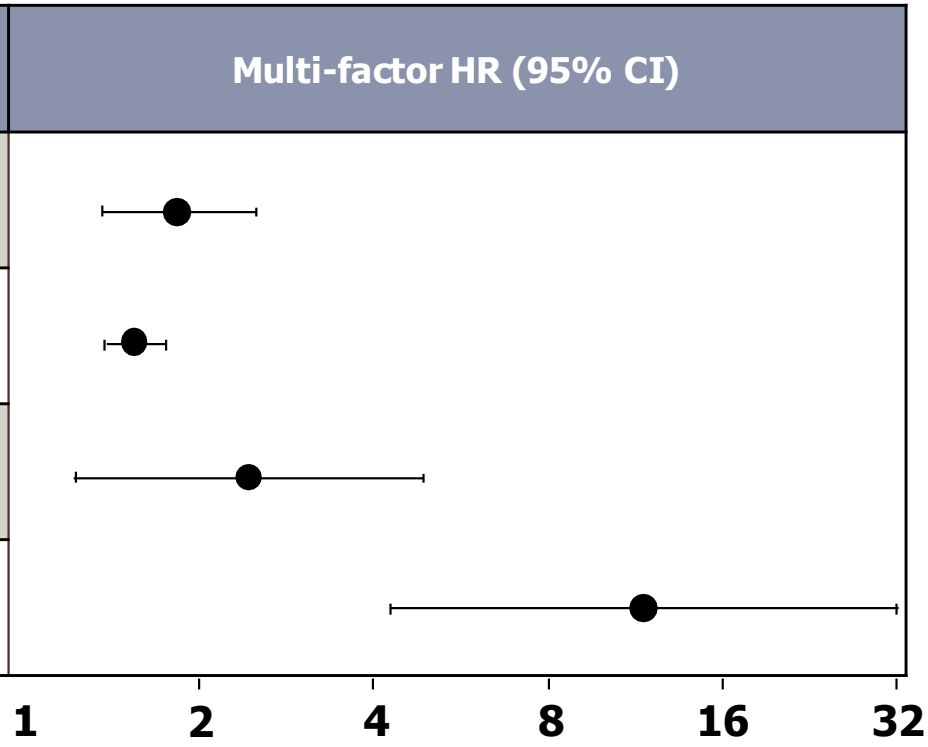
5 **Permanent discontinuations of BARI due to DVT/PE**

1 **Fatal PE**

[a]IR per 100 PYE; Note: PYE=PYR (patient years at risk), where exposure is censored at the time of event; [b]The two patients with recurrence had recent risk factors (prior surgery and discontinuation of warfarin); 1. www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/arthritisadvisorycommittee/ucm605062.pdf; 2. Data on file, Eli Lilly and Company

Multi-variable risk analysis: DVT/PE (All BARI RA)[1]

Characteristic	Patients with DVT/PE (N=42)	Patients without DVT/PE (N=3450[a])	Multi-factor HR (95% CI)
Age (for every 10 year increase)	–	–	
BMI for every 5 kg/m^2 increase	–	–	
COX-2 inhibitor use, n (%)	11 (26)	487 (14)	
History of DVT/PE, n (%)	4 (9.5)	30 (0.9)	

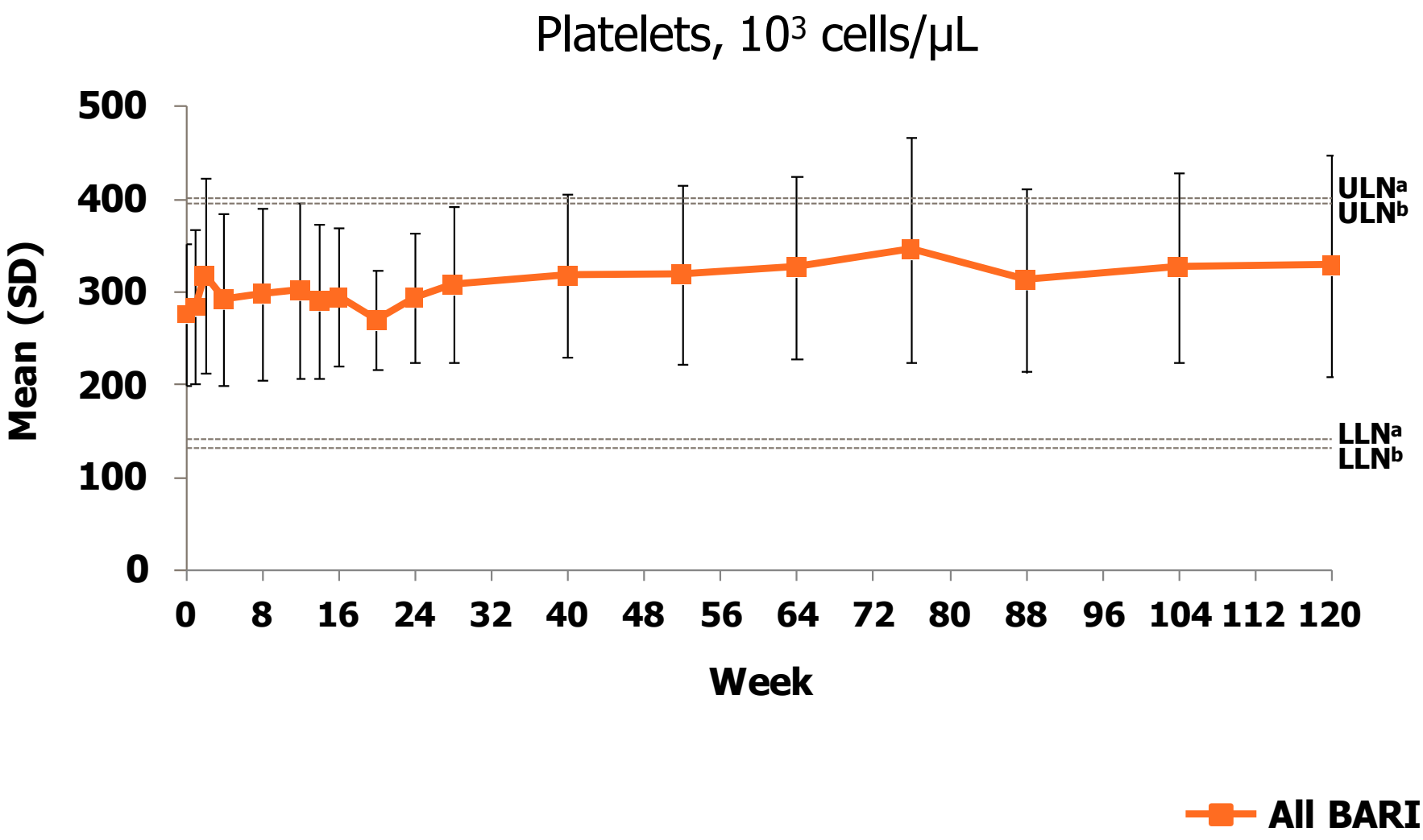


The magnitude of DVT/PE risk increase for COX-2 inhibitor use is similar to the published risk ratio in the general population[2]

[a]N=3446 for BMI; BMI=body mass index; COX-2=cyclooxygenase 2; DVT=deep vein thrombosis; HR=hazard ratio; PE=pulmonary embolism; RA=rheumatoid arthritis; 1. Weinblatt M et al. Presented at ACR 2018. Abstract 2815; 2. Ungprasert P et al. *Rheumatology* 2015;54(4): 736-42

Platelets over time: Patients with DVT/PE event

BARI BARICITINIB 19 MU
April 1, 2017

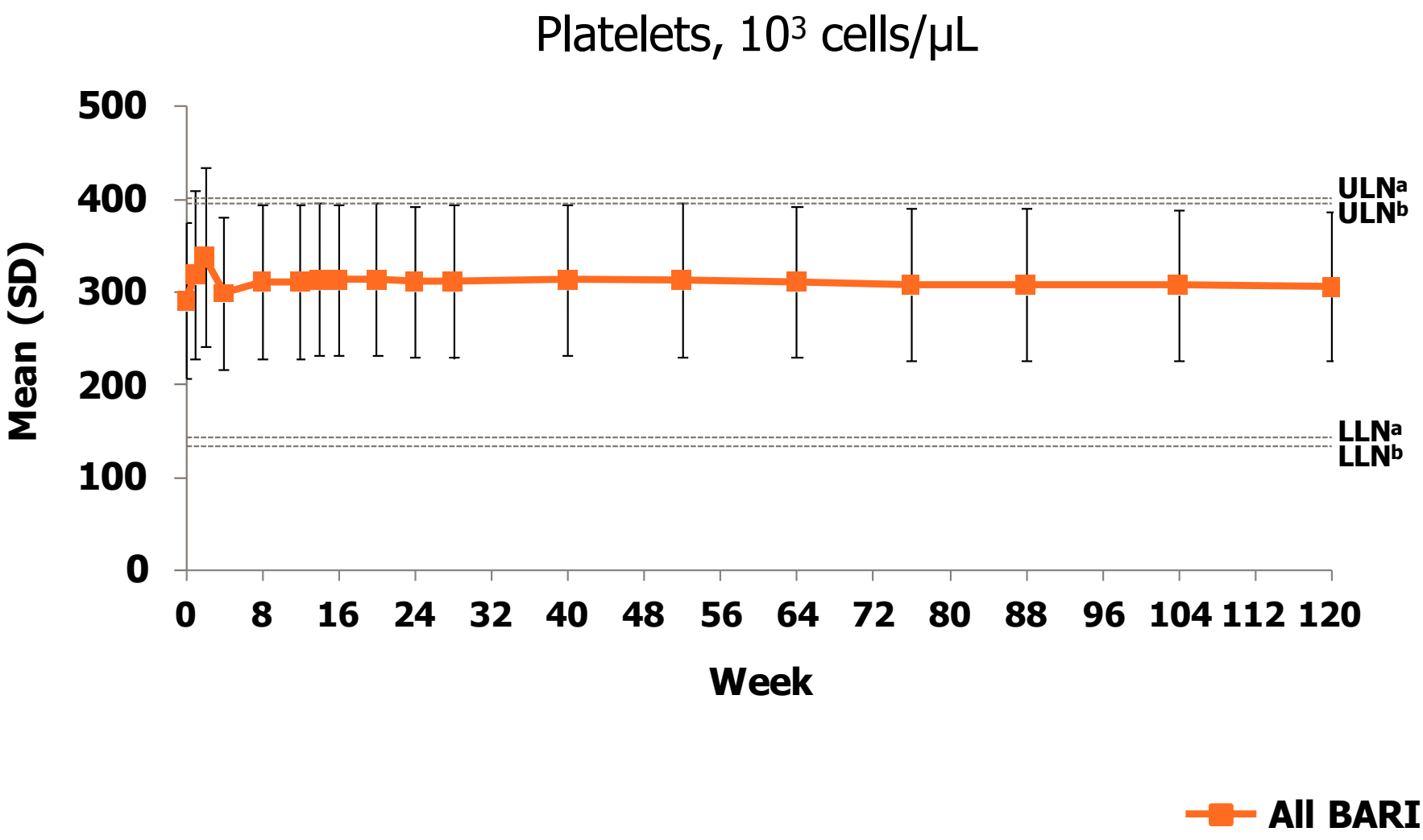


[a]Age <60 years; [b]Age ≥60 years

DVT=deep vein thrombosis; LLN=lower limit of normal; MU=month update; PE=pulmonary embolism; RA=rheumatoid arthritis; ULN=upper limit of normal; Data on file, Eli Lilly and Company

Platelets over time: Patients without DVT/PE event

BARI BARICITINIB 19 MU
April 1, 2017

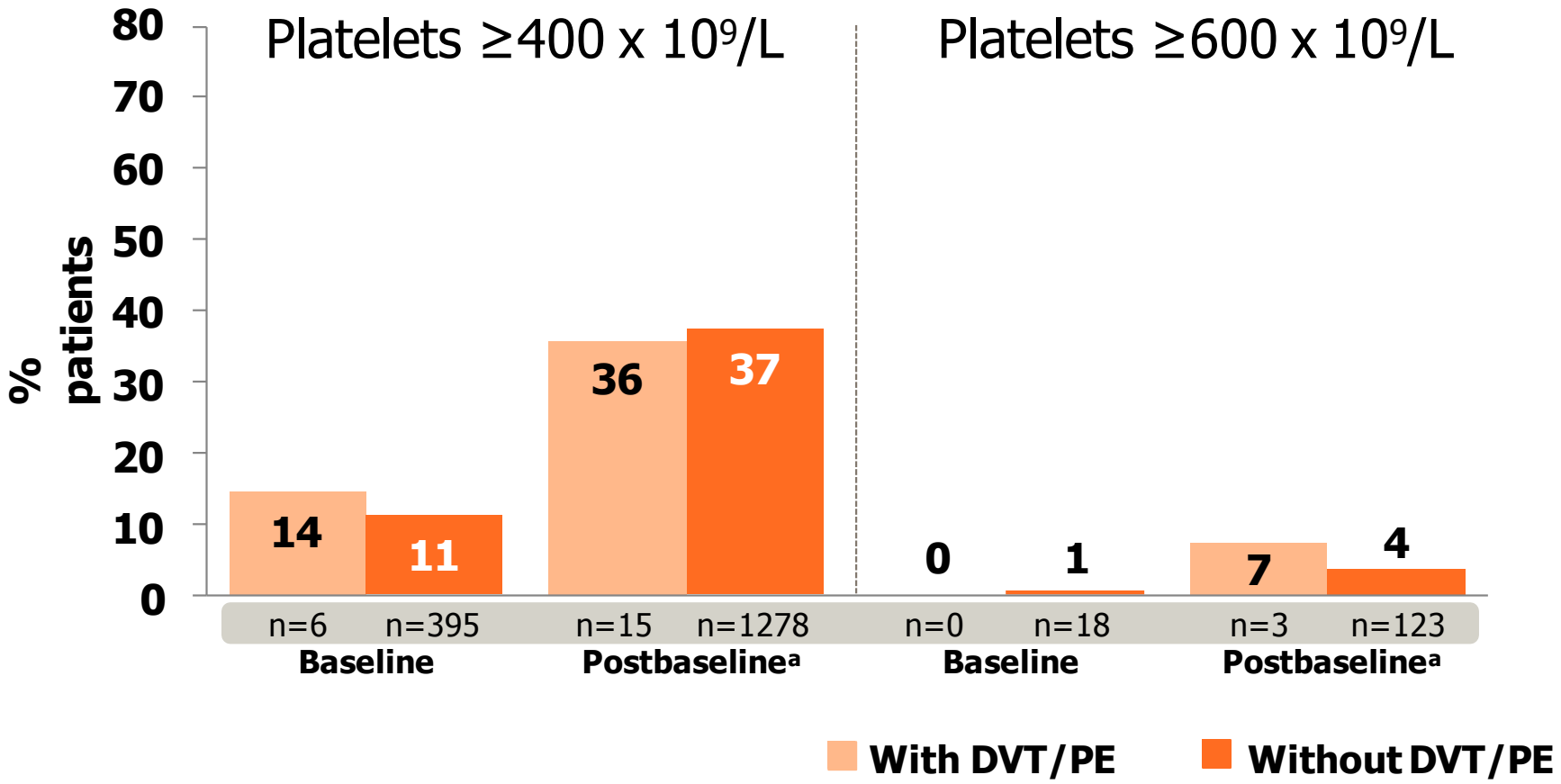


[a]Age <60 years; [b]Age ≥60 years

DVT=deep vein thrombosis; LLN=lower limit of normal; MU=month update; PE=pulmonary embolism; RA=rheumatoid arthritis; ULN=upper limit of normal; Data on file, Eli Lilly and Company

Thrombocytosis in patients with or without DVT/PE: All BARI RA

The proportion of patients with high platelet levels was comparable between patients **with** DVT/PE versus those **without** DVT/PE



[a]Highest at any time post-baseline prior to the event. DVT=deep vein thrombosis; MU=month update; PE=pulmonary embolism; RA=rheumatoid arthritis. 1. Data on file, Eli Lilly and Company; 2. Kremer J et al. Presented at EULAR 2017. Abstract 1325

Mean Platelet Volume: A Link Between Thrombosis and Inflammation?

AY Gasparyan *et al*. Current Pharmaceutical Design 2011 Jan; 17(1):47-58

- Correlation between an **increase in MPV** and the **risk of thrombosis**
- **High MPV** associates with a variety of established risk factors, cardio- and cerebrovascular disorders, and **low-grade inflammatory** conditions prone to arterial and venous thromboses
- **High-grade inflammatory** diseases, such as active rheumatoid arthritis or attacks of familial Mediterranean fever, present with **low levels of MPV**, which ***reverse in the course of anti-inflammatory therapy***

Summary and conclusions

MACE, ATE, CHF

- Similar between placebo and Baricitinib
- MACE IR of 0.5 similar to rates observed with other DMARDs
- No association between increased lipids and MACE

VTE

- Recognized risk in RA
- Totality of evidence does not support an association with Baricitinib, but a causal relationship can't be entirely ruled out
- Ongoing PV, RW-studies, and post-marketing RCTs will bring much more evidence to bear toward this assessment in the future