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creating better medicines

Compelling topline results from the Phase IIb combination therapy study of vobarilizumab, ALX-0061 (anti-IL-6R), in patients with moderate to severe RA

9 August 2016

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Vobarilizumab Phase IIb RA combination therapy study

Participants on the call

Dr Edwin Moses

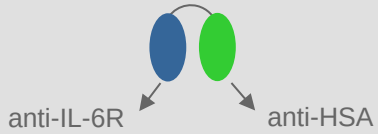
CEO

Dr Robert K. Zeldin

CMO

Vobarilizumab

Unique half-life extended Nanobody product

Features	Potential benefits
Small (26kD) 	• Penetrates faster and more effectively into tissues
Targets human serum albumin	• Prolongs half-life • Improved trafficking to inflamed tissue
Monovalent binding	• Avoids target cross-linking
Preferential binding of soluble vs. membrane bound IL-6R	• Superior benefit/risk profile
Strong affinity to soluble IL-6R	• Fast target engagement resulting in fast onset of action
Tailored PK	• Extended therapeutic window • Convenient dosing and scheduling

Anti-IL-6R Nanobody – ALX-0061, vobarilizumab

Potential best-in-class treatment for Rheumatoid Arthritis (RA)

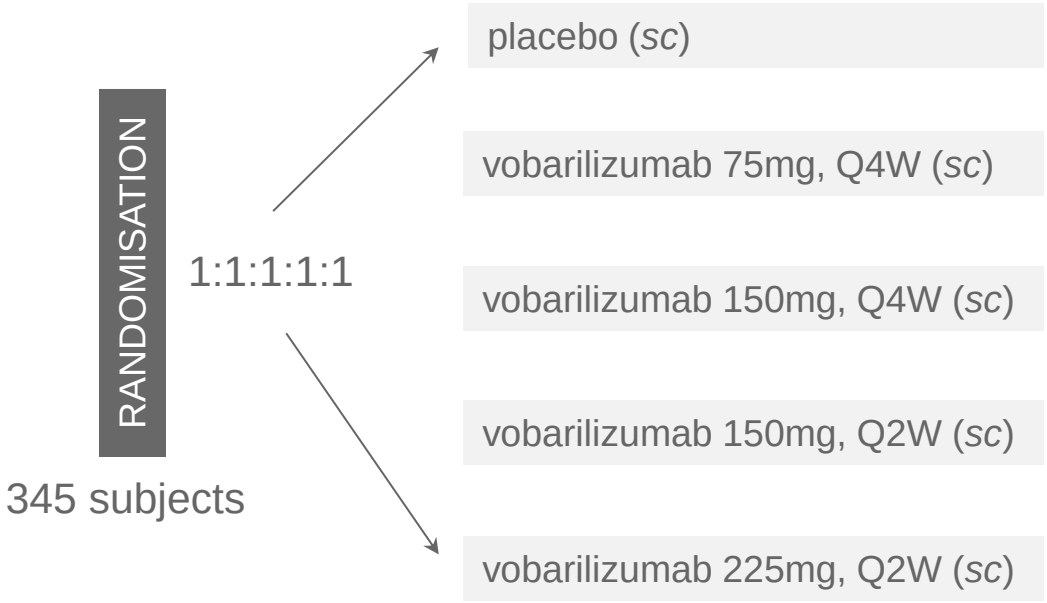
- **Best-in-class potential** for the treatment of RA
- Global option licensing deal with **AbbVie**
- Positive topline results for **Phase IIb monotherapy and combination therapy studies** in a total of ~600 RA patients
- **Open-label extension** study ongoing in **RA** patients
- **Phase II** study in **SLE** patients ongoing

RA: rheumatoid arthritis
SLE: systemic lupus erythematosus

Vobarilizumab (ALX-0061)

Phase IIb RA combination study with methotrexate* in 345 patients

- Adults with moderate to severe RA despite MTX therapy (stable dose of 12.5–25 mg/week for at least 6 consecutive weeks prior screening)
- Randomised, double-blind, placebo-controlled 24 week dose ranging study in Europe, Latin America and the US
- Forced discontinuation based on less than 20% improvement in both swollen and tender joint counts at weeks 12, 16 and 20
- Recruitment from March 2015 to December 2015



Primary endpoint at week 12:
ACR20 response

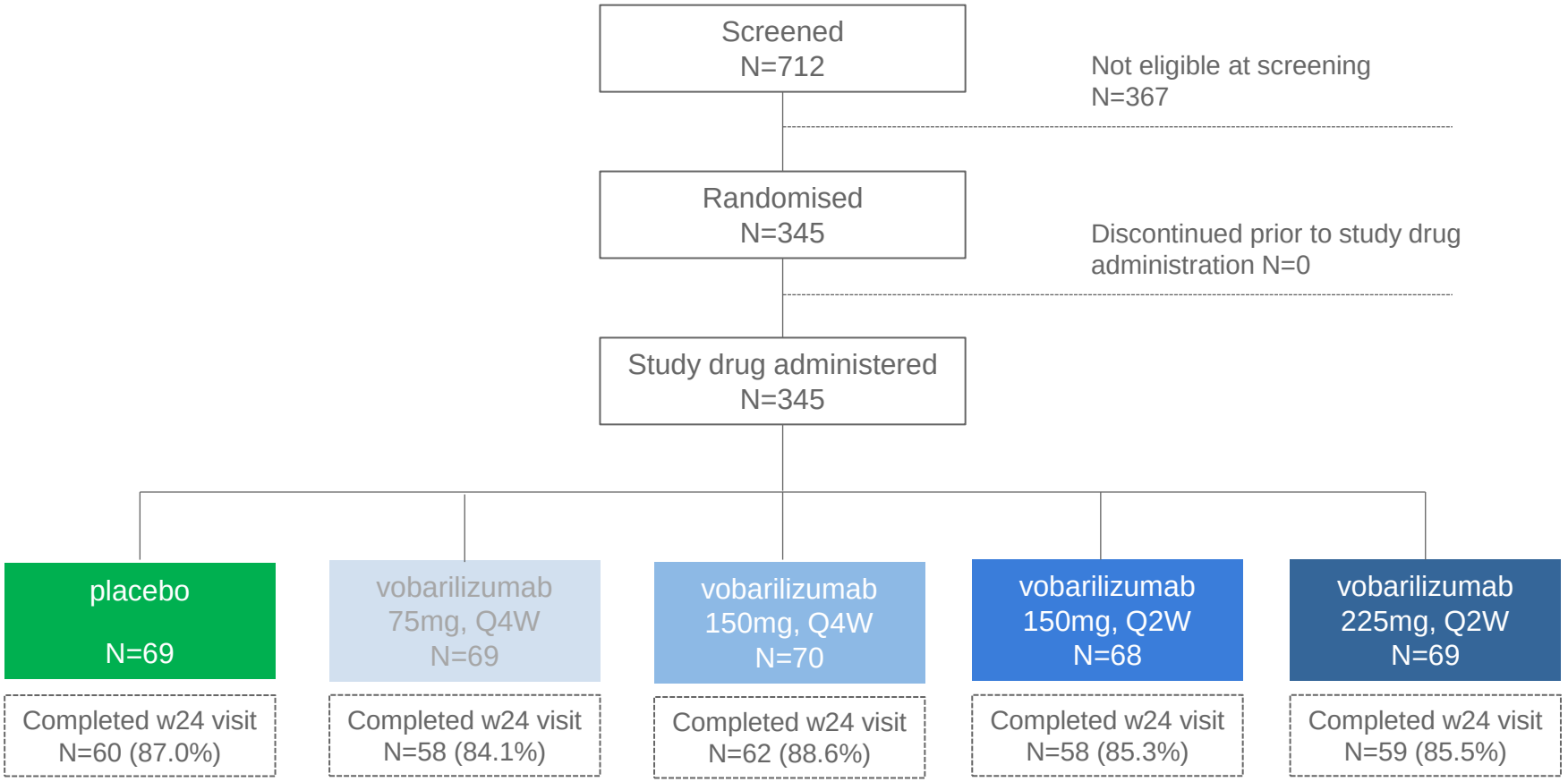
Secondary endpoints:
ACR responses over time, disease activity scores, EULAR DAS28 response, remission, effects on quality of life

Other assessments:
pharmacokinetics, pharmacodynamics, safety/tolerability, immunogenicity

* MTX

Vobarilizumab Phase IIb RA combination therapy study

Patient disposition



A high proportion of patients completed the 24-week treatment period
94% of eligible patients rolled over into the open-label extension study

Vobarilizumab Phase IIb RA combination therapy study

Baseline demographics and disease activity – ITT population

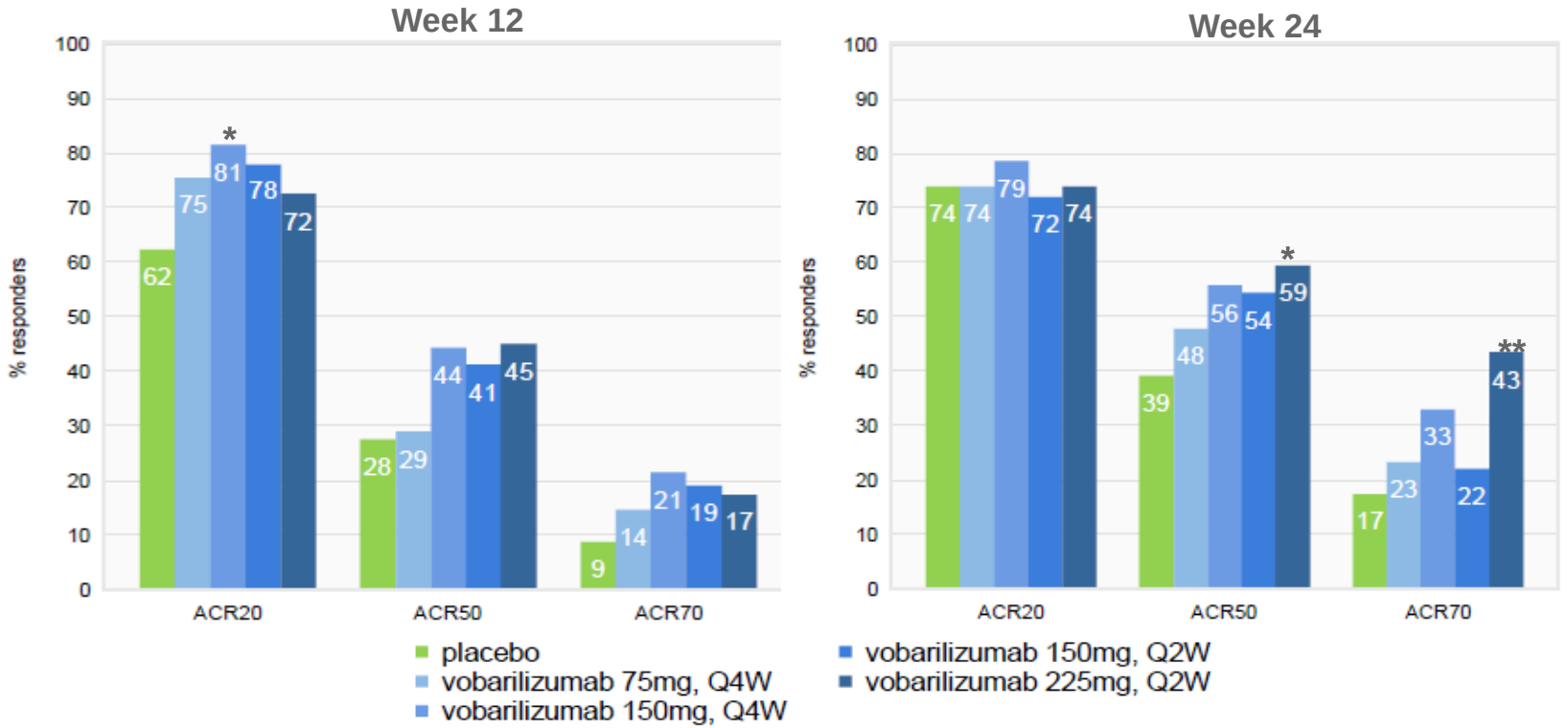
Mean (SD)	placebo N=69	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N=70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
Age, years	52.8 (11.9)	53.3 (10.4)	52.0 (13.2)	51.9 (11.9)	52.3 (13.4)
Females (%)	79.7	84.1	88.6	86.8	79.7
Duration of RA, years	7.4 (7.0)	7.3 (6.8)	8.9 (9.8)	8.6 (7.8)	8.0 (8.1)
TJC68	24.9 (12.7)	25.9 (12.3)	24.2 (12.3)	26.5 (13.8)	23.9 (13.4)
SJC66	17.0 (10.0)	16.3 (7.3)	15.1 (8.5)	17.8 (9.5)	15.4 (10.0)
CRP, mg/L	20.3 (22.5)	19.1 (19.6)	20.7 (22.6)	25.3 (36.3)	17.8 (18.8)
$DAS28_{CRP}$	6.0 (0.9)	6.0 (0.8)	5.8 (0.9)	6.1 (0.9)	5.8 (0.9)
HAQ-DI score	1.7 (0.5)	1.7 (0.7)	1.6 (0.6)	1.8 (0.7)	1.6 (0.7)
MTX, mg/week	15.9 (3.5)	17.4 (4.2)	17.3 (4.2)	16.2 (3.4)	17.3 (4.6)

Baseline demographics reflective of a typical RA population with similar disease profiles across the groups

ITT, intent-to-treat; TJC, tender joint count; SJC, swollen joint count; CRP, C-reactive protein; $DAS28_{CRP}$, disease activity score in 28 joints using CRP; HAQ-DI, health assessment questionnaire disability score for RA

Vobarilizumab Phase IIb RA combination therapy study

ACR20/50/70 responses at weeks 12 and 24 – ITT population



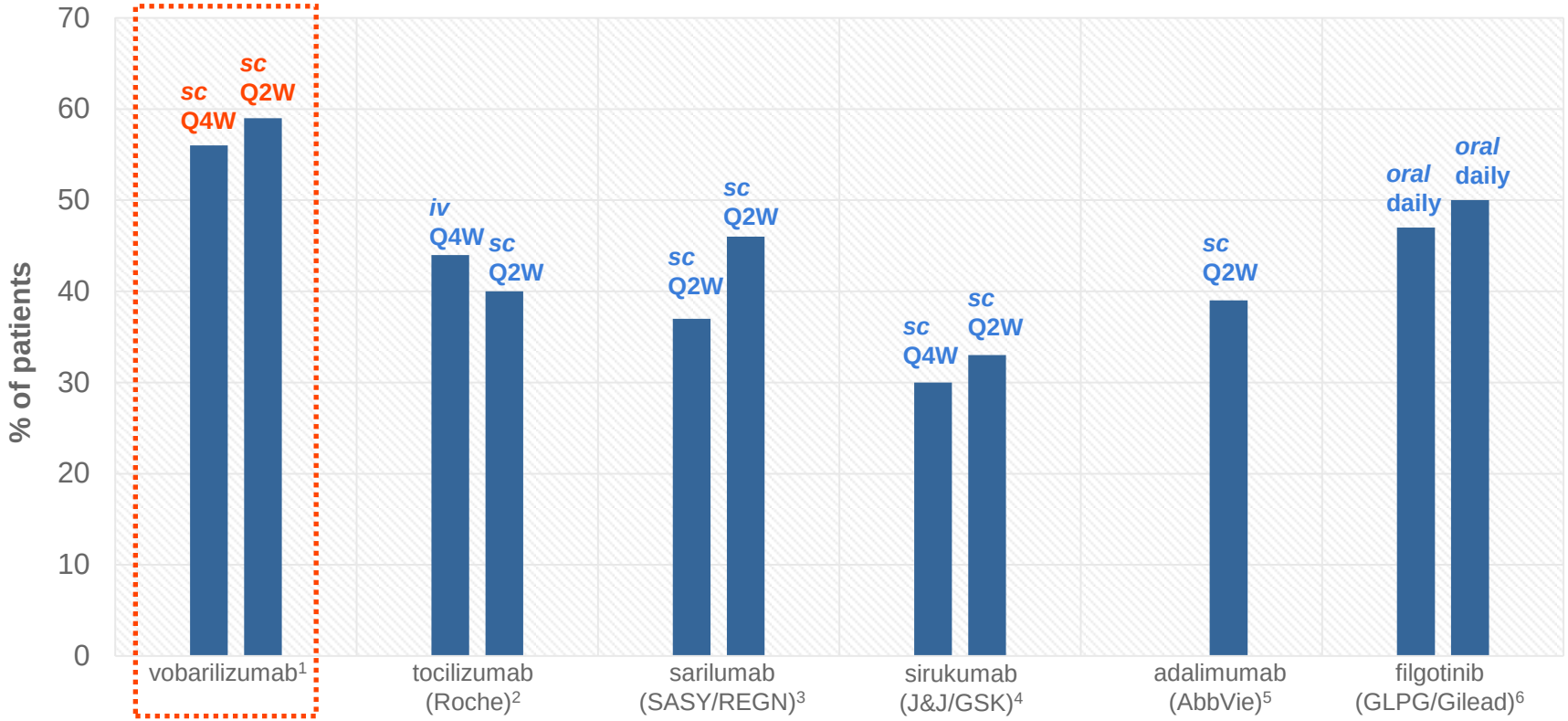
* nominal p<0.05 vs. placebo; ** nominal p<0.01 vs placebo

Response rates of vobarilizumab are consistent with previous studies
Continued improvement in ACR50 and ACR70 scores from 12 to 24 weeks
Opportunity for monthly dosing confirmed

Vobarilizumab has the potential to be best of all classes

ACR50 scores at week 24 – RA combination therapy studies

Note: data reported in listed publications, not resulting from head-to-head studies

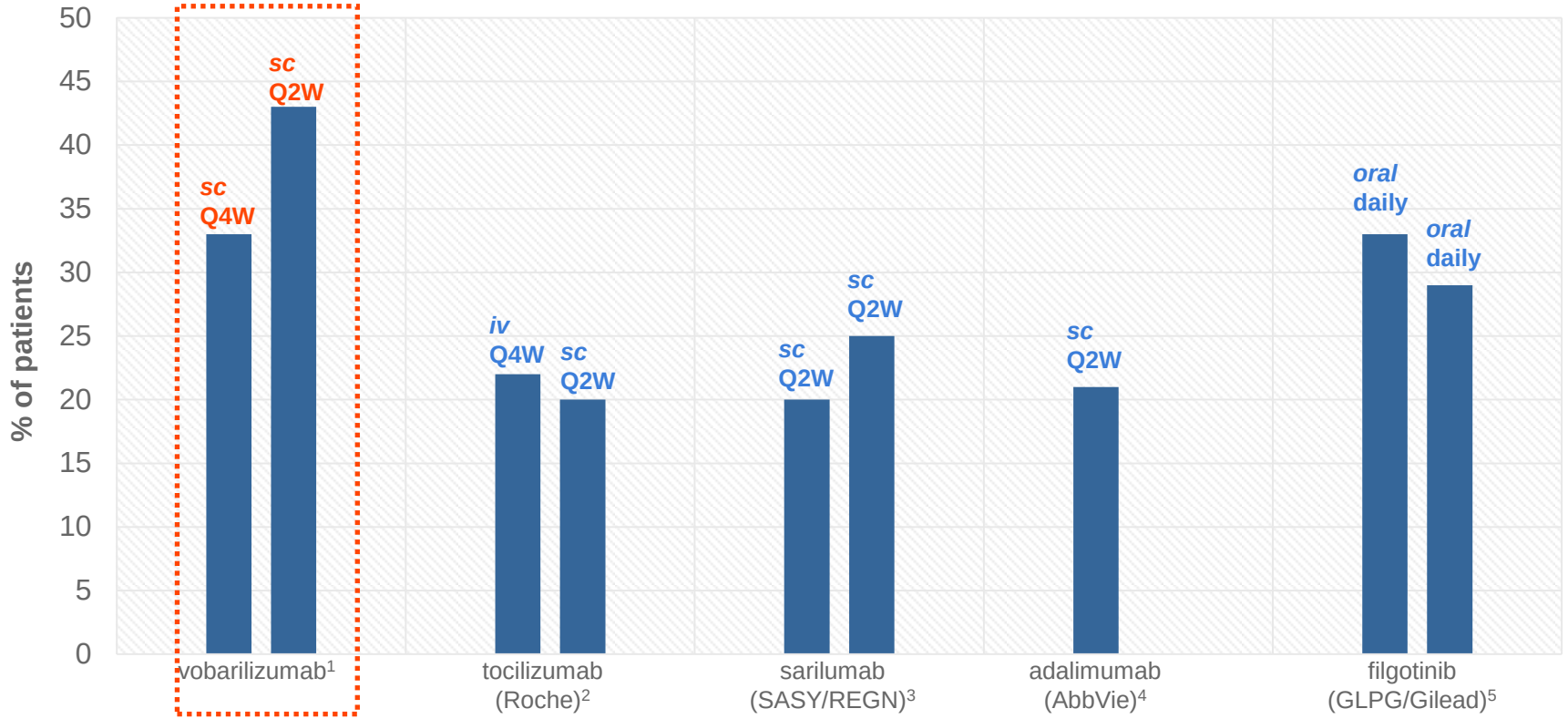


[1] PhIIb: (sc) 150mg Q4W and 225mg Q2W + MTX; [2] OPTION PhIII: (iv) 8mg/kg Q4W + MTX and BREVACTA PhIII (sc) 162mg Q2W + MTX; [3] MOBILITY PhIII: (sc) 150 mg Q2W and 200mg Q2W + MTX; [4] PhIII: (sc) 50mg Q4W and 100mg Q2W + csDMARDs [5] 2003 FDA briefing document: DE019 Ph II/III: (sc) 40mg Q2W +MTX; [6] DARWIN 1 PhIIb: (oral) 100mg QD, 200mg QD + MTX

Vobarilizumab has the potential to be best of all classes

ACR70 scores at week 24 – RA combination therapy studies

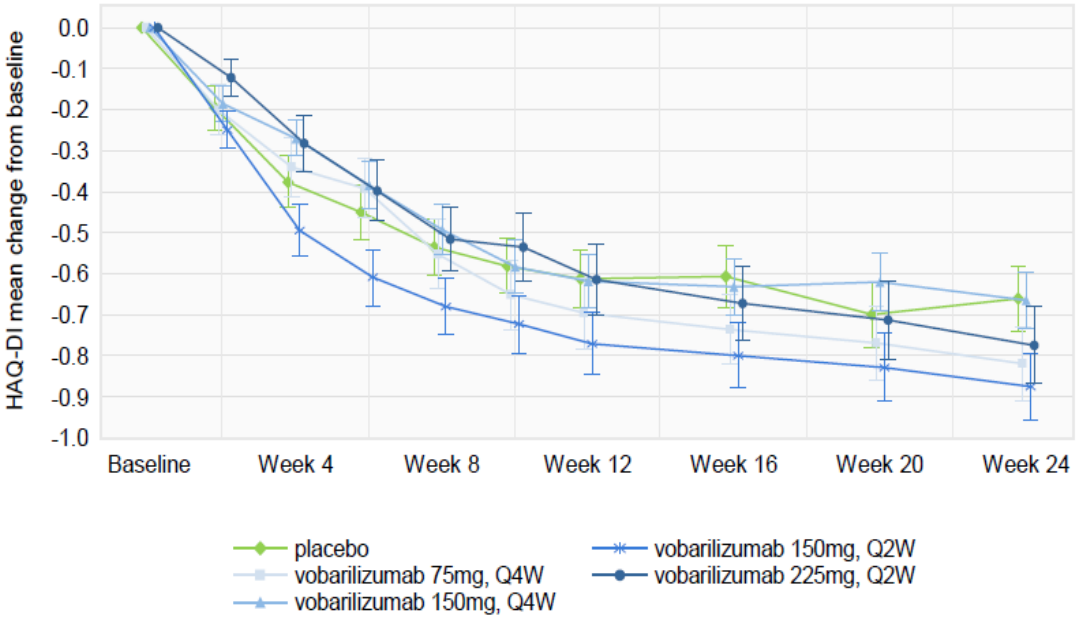
Note: data reported in listed publications, not resulting from head-to-head studies



[1] PhIIb: (sc) 150mg Q4W and 225mg Q2W + MTX; [2] OPTION PhIII: (iv) 8mg/kg Q4W + MTX and BREVACTA PhIII (sc) 162mg Q2W + MTX; [3] MOBILITY PhIII: (sc) 150 mg Q2W and 200mg Q2W + MTX; [4] 2003 FDA briefing document: DE019 Ph II/III: (sc) 40mg Q2W +MTX; [5] DARWIN 1 PhIIb: (oral) 100mg QD, 200mg QD + MTX; [6] BALANCE-2 PhIIb: oral 6mg BID, 12mg BID + MTX

Vobarilizumab Phase IIb RA combination therapy study

HAQ-DI improvement and change from baseline – ITT population



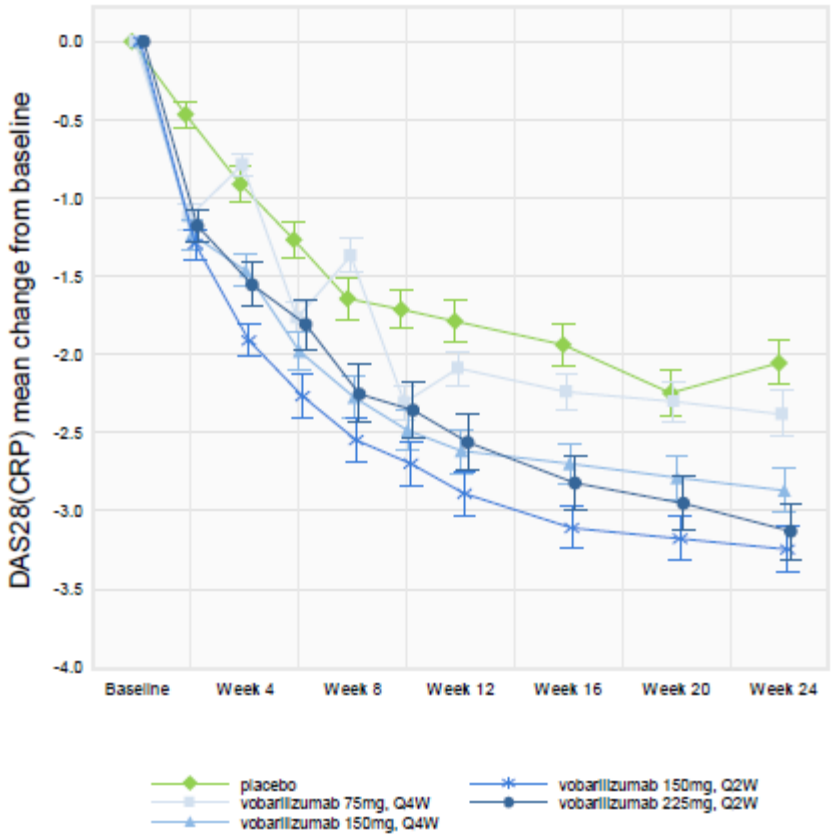
Patients treated with vobarilizumab experience a rapid improvement in their physical function

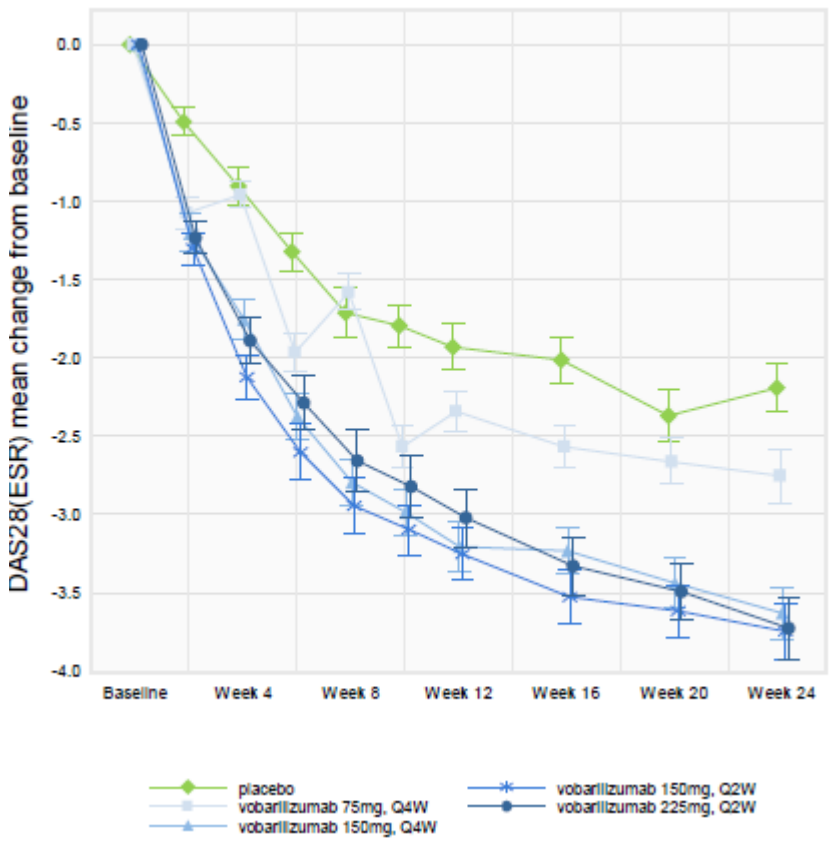
	placebo N=69	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N=70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
% with a clinically meaningful improvement in HAQ-DI score *(≥0.25) at week 24	71%	68%	67%	68%	65%
Absolute change from baseline at week 12 (mean)	-0.61	-0.70	-0.62	-0.77	-0.62
Absolute change from baseline at week 24 (mean)	-0.66	-0.82	-0.67	-0.88	-0.77

* Wolfe F. *et al*, Arthritis & Rheumatism, Vol. 42, No. 9, September 1999, pp 1797–1808

Vobarilizumab Phase IIb RA combination therapy study

Change in $DAS28_{CRP}$ and $DAS28_{ESR}$ from baseline



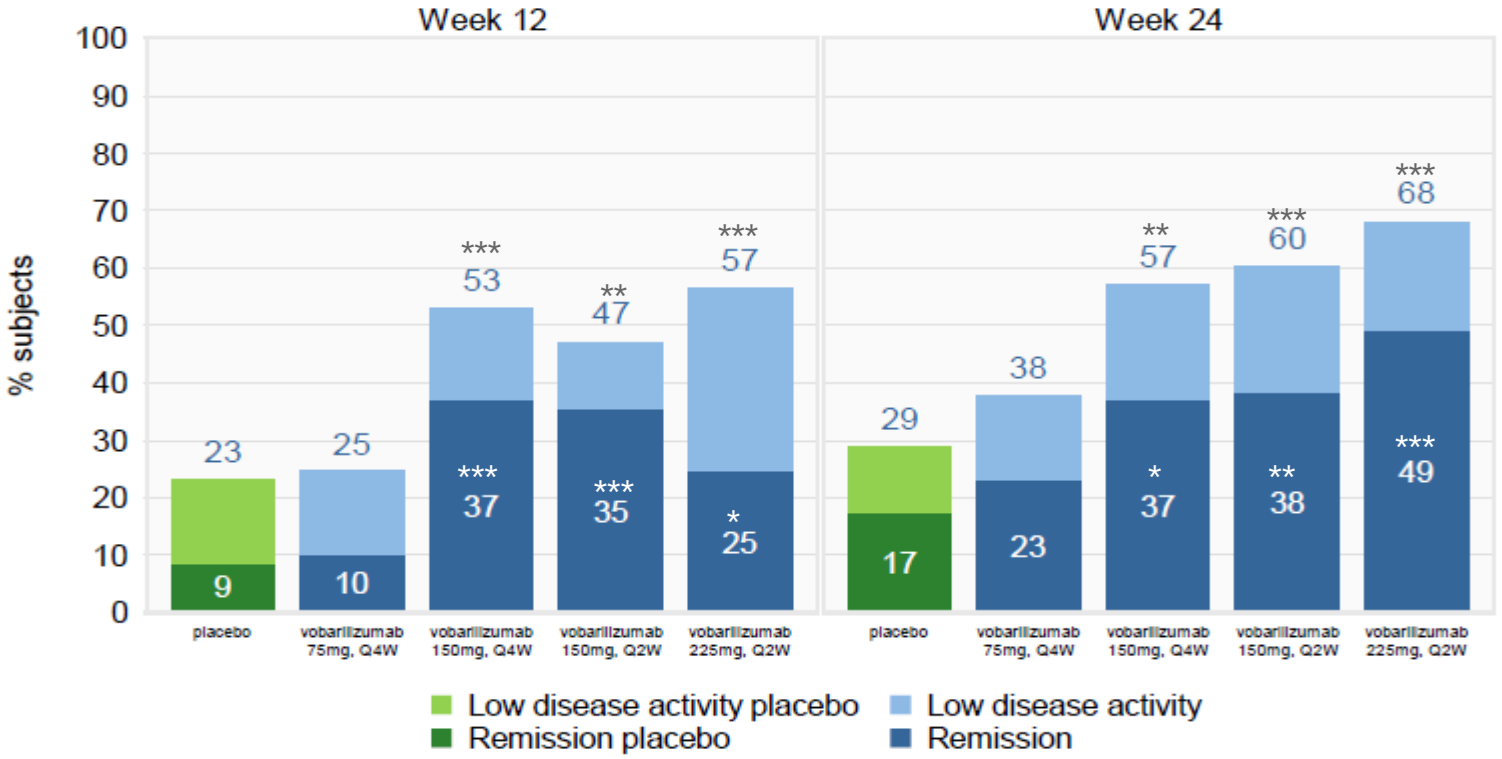


Vobarilizumab rapidly reduces disease activity and its effect is sustained through to week 24

ESR, erythrocyte sedimentation rate; $DAS28_{ESR}$, disease activity score to measure disease activity based on ESR

Vobarilizumab Phase IIb RA combination therapy study

Remission and low disease activity – ITT population



* nominal p<0.05 vs. placebo; ** nominal p<0.01 vs. placebo; *** nominal p<0.001 vs. placebo

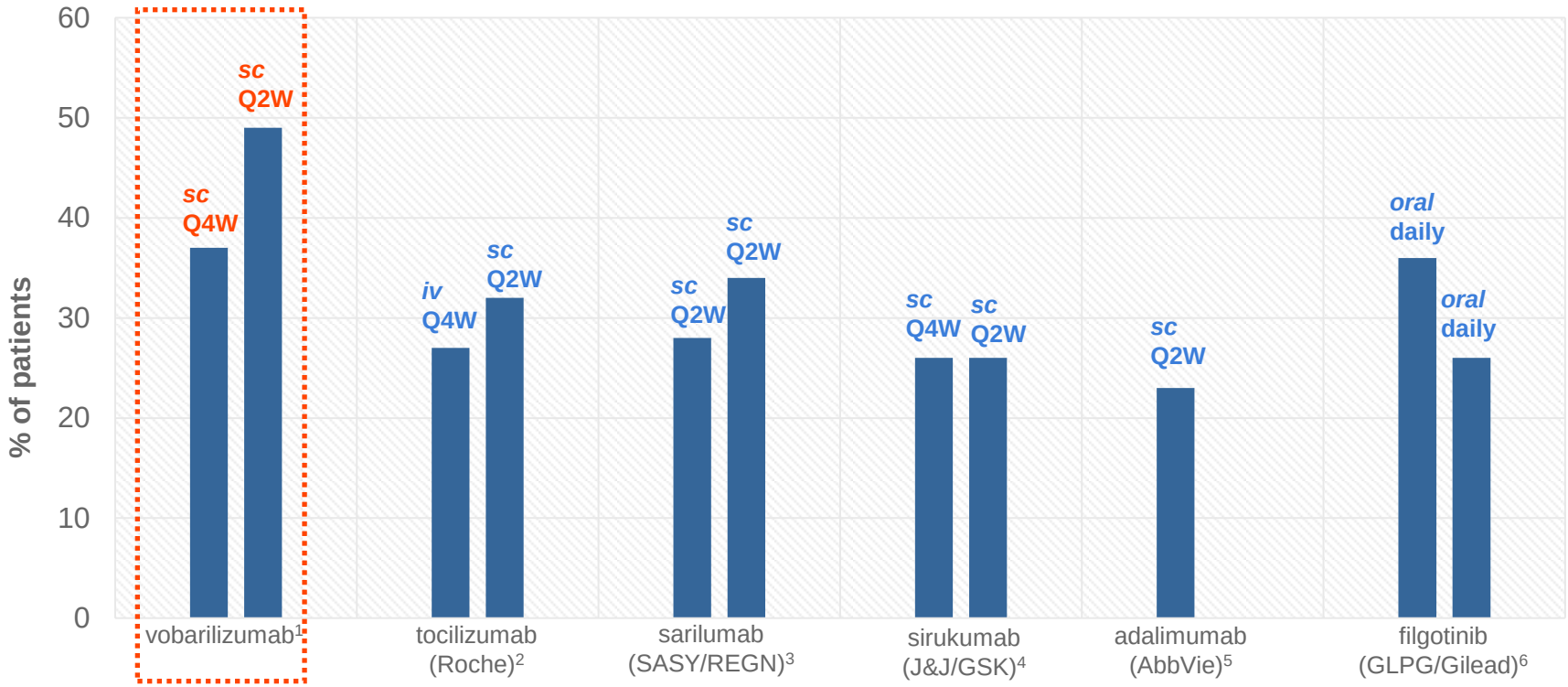
Strikingly, up to 49% of patients in clinical remission at week 24, confirming vobarilizumab's best-in-class efficacy profile

Remission: $DAS28_{CRP}$ < 2.6; low disease activitiy: 2.6 ≤ $DAS28_{CRP}$ ≤ 3.2

Vobarilizumab has the potential to be best of all classes

Remission ($DAS28_{CRP}$<2.6) at week 24 – RA combination therapy studies

Note: data reported in listed publications, not resulting from head-to-head studies



[1] PhIIb: (sc) 150mg Q4W and 225mg Q2W + MTX; [2] Data from OPTION PhIII: (iv) 8mg/kg Q4W + MTX and BREVACTA PhIII (sc) 162mg Q2W + MTX; [3] MOBILITY PhIII: (sc) 150 mg Q2W and 200mg Q2W + MTX; [4] PhIII: (sc) 50mg Q4W and 100mg Q2W + csDMARDs; [5] Weinblatt *et al*, Arthritis & Rheumatology, Sept 2015; [6] DARWIN 1: (oral) 100mg QD, 200mg QD + MTX; [7] BALANCE-2 PhIIb: oral 6mg BID, 12mg BID + MTX

Vobarilizumab Phase IIb RA combination therapy study

Safety results through week 24

Number of subjects (%) with treatment-emergent adverse events (TEAE)	placebo N=69	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N= 70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
Any TEAE	**36 (52.2%)**	**42 (60.9%)**	**44 (62.9%)**	**43 (63.2%)**	**44 (63.8%)**
- treatment-related	18 (26.1%)	26 (37.7%)	25 (35.7%)	25 (36.8%)	25 (36.2%)
- leading to study drug discontinuation	3 (4.3%)	4 (5.8%)	5 (7.1%)	5 (7.4%)	4 (5.8%)
Any serious TEAE	**4 (5.8%)**	**5 (7.2%)**	**4 (5.7%)**	**0**	**1 (1.4%)**
- treatment-related	2 (2.9%)	1 (1.4%)	3 (4.3%)	0	1 (1.4%)
- leading to death (not treatment-related)	1 (0.3%)				

Excellent safety profile confirmed across a larger patient population

Vobarilizumab Phase IIb RA combination therapy study

Safety laboratory data through week 24

% of subjects	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N=70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
Aspartate aminotransferase				
>3 – ≤5 x ULN (grade 2)	1.4%	2.9%	7.5%	1.4%
>5 – ≤20 x ULN (grade 3)	1.4%	0%	0%	1.4%
Alanine aminotransferase				
>3 – ≤5 x ULN (grade 2)	2.9%	2.9%	3.0%	4.3%
>5 – ≤20 x ULN (grade 3)	2.9%	1.4%	3.0%	0%
Absolute neutrophil count				
<1.5 to 1.0 x 10^9/L (grade 2)	8.7%	7.2%	9.0%	8.7%
<1.0 to 0.5 x 10^9/L (grade 3)	1.4%	1.4%	1.5%	0%
Absolute platelet count				
<75.0 to 50.0 x 10^9/L (grade 2)	0%	0%	1.5%	0%
<50.0 to 25.0 x 10^9/L (grade 3)	0%	0%	0%	0%

Laboratory assessments confirm vobarilizumab's positively differentiated safety profile

Data for the placebo group not communicated in order to keep the study blind

Vobarilizumab Phase IIb RA combination therapy study

LDL/HDL cholesterol ratio

Mean (SD) LDL/HDL ratio	placebo N=69	vobarilizumab 75mg, Q4W N=69	vobarilizumab 150mg, Q4W N=70	vobarilizumab 150mg, Q2W N=68	vobarilizumab 225mg, Q2W N=69
Baseline	2.49 (0.78)	2.31 (0.77)	2.34 (0.66)	2.27 (0.92)	2.22 (0.71)
Week 12	2.53 (0.82)	2.26 (0.73)	2.40 (0.85)	2.37 (1.16)	2.23 (0.75)
Week 24	2.39 (0.78)	2.30 (0.77)	2.26 (0.72)	2.25 (0.92)	2.13 (0.72)

At all doses tested, vobarilizumab had no effect on the mean LDL/HDL cholesterol ratio, which further confirms its positively differentiated safety profile

Vobarilizumab has the potential to be best of all classes

Efficacy results from various RA combination therapy studies

Note: 24w data reported in listed publications, not resulting from head-to-head studies

Compound	Dose	Stage	ACR50	ACR70	DAS28 remission*
vobarilizumab	150mg Q4W	PhIIb	56%	33%	37%
vobarilizumab	150mg Q2W	PhIIb	54%	22%	38%
vobarilizumab	225mg Q2W	PhIIb	59%	43%	49%
tocilizumab iv [1]	8mg/kg	market	44%	22%	27%
tocilizumab sc [2]	162mg Q2W	market	40%	20%	32%
sarilumab [3]	150mg Q2W	BLA Oct'15	37%	20%	28%
sarilumab [3]	200mg Q2W	BLA Oct'15	46%	25%	34%
sirukumab [4]	50mg Q4W	BLA in 2016e	30%	Not reported	26%
sirukumab [4]	100mg Q2W	BLA in 2016e	33%	Not reported	26%
adalimumab [5]	40mg Q2W	market	39%	21%	24% [7]
filgotinib [6]	100mg QD	PhIII in 2016e	47%	33%	36%
filgotinib [6]	200mg QD	PhIII in 2016e	50%	29%	26%

(*) based on CRP (except for tocilizumab sc: based on ESR; tocilizumab iv: CRP/ESR is not specified in publication)

1. Smolen et al., 2008, The Lancet, 371, 987-97
2. Kivitz at al., 2014, Arthr. Care & Res., 66, 1653-61
3. Genovese et al., 2015, Arthritis Rheumatol., 67, 1424-37
4. Takeuchi et al., EULAR 2016, Abstract # SAT0145
5. FDA briefing document
6. Westhovens et al., EULAR 2016, Abstract & oral presentation # OP0224, and Webcast Galapagos 30 July 2015
7. Weinblatt et al., 2015, Arthritis Rheumatol., 67, 2591-600

Vobarilizumab has the potential to be best of all classes

Safety results from various RA combination therapy studies

Note: data reported in listed publications, not resulting from head-to-head studies

Compound	Dose	Stage	Pts with ≥1 SAE	Pts with ≥1 serious infection	Pts with ALT grade 2 toxicity	Pts with ALT grade 3 toxicity	Pts with neutropenia grade 3 toxicity
vobarilizumab (24w)	150mg Q4W	PhIIb	5.7%	2.9%	2.9%	1.4%	1.4%
vobarilizumab (24w)	150mg Q2W	PhIIb	0%	0%	3.0%	3.0%	1.5%
vobarilizumab (24w)	225mg Q2W	PhIIb	1.4%	1.4%	4.3%	0%	0%
tocilizumab iv (24w) [1]	8mg/kg iv	market	6%	3%	10%	3.4%	Not reported
tocilizumab sc (24w) [2]	162mg Q2W	market	4.6%	2.1%	1.6%	0.2%	3.5%
sarilumab (52w) [3]	150mg Q2W	BLA Oct'15	8.8%	2.6%	9.5%	Not reported	5.1%
sarilumab (52w) [3]	200mg Q2W	BLA Oct'15	11.3%	4.0%	8.0%		7.8%
sirukumab (18w) [4]	50mg Q4W	BLA in 2016e	2.9%	0.7%	Not reported	3.2%	4.1 %
sirukumab (18w) [4]	100mg Q2W	BLA in 2016e	4.7%	0.9%	Not reported		
adalimumab [5]	40mg Q2W	Market	5.1%	0.04/patient year [7]	0%	0%	1.9%
filgotinib (24w) [6]	100mg QD	PhIII in 2016e	5%	4%	Not reported	0%	0%
filgotinib (24w) [6]	200mg QD	PhIII in 2016e	2%	1%	Not reported	0%	1.2%

1. Smolen et al., 2008, The Lancet, 371, 987-97
2. Kivitz at al., 2014, Arthr. Care & Res., 66, 1653-61
3. Genovese et al., 2015, Arthritis Rheumatol., 67, 1424-37
4. Takeuchi et al., EULAR 2016, Abstract # SAT0145
5. Weinblatt et al., 2015, Arthritis Rheumatol., 67, 2591-600
6. Westhovens et al., EULAR 2016, Abstract & oral presentation # OP0224, and Webcast Galapagos 30 July 2015
7. SmPC Humira®

Vobarilizumab Phase IIb RA combination therapy study

Conclusions from topline results

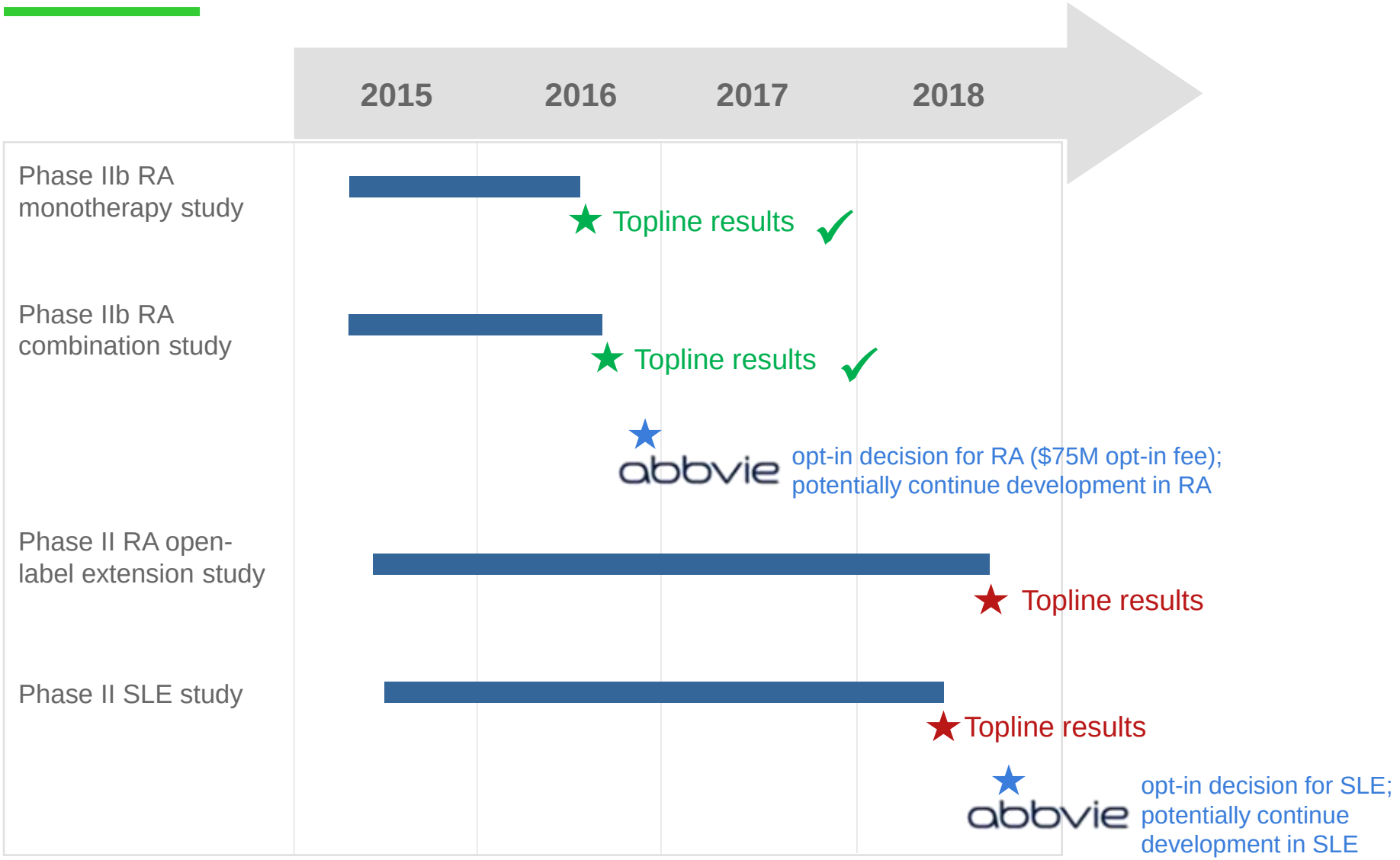
- High ACR20, ACR50 and ACR70 responses of up to 79%, 59% and 43% at week 24
- Rapid, strong and sustained reduction in disease activity
  - up to 37% of patients in clinical remission at week 12
  - up to 49% of patients in clinical remission at week 24
- Highly efficacious with less frequent dosing as compared to other anti-IL-6/IL-6R drugs
- Excellent safety profile at all administered doses with a clear advantage compared to other anti-IL-6R drugs
- Vobarilizumab has the potential to be best of all classes in RA

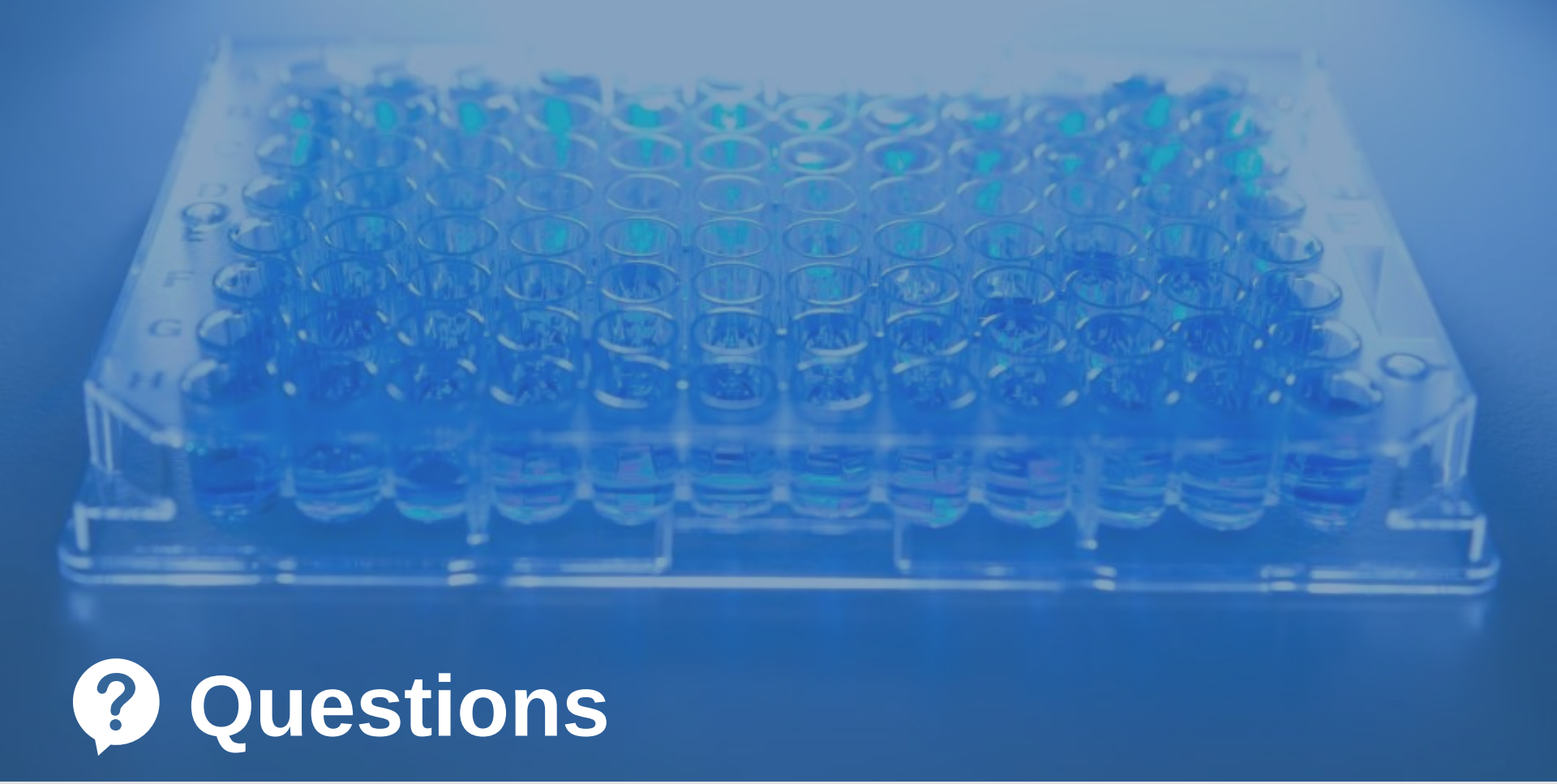
Striking efficacy and safety profile

Final data analysis ongoing

Vobarilizumab

Key upcoming catalysts





Questions

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Addendum

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Vobarilizumab (ALX-0061)

Positive topline results reported in previous studies

- Highly efficacious

Signs and symptoms of RA	Phase IIa combination therapy study – week 24	Phase IIb monotherapy study – week 12		
	All responders (pooled)	150mg, Q4W	150mg, Q2W	225mg, Q2W
ACR20	83%	73%	77%	81%
ACR50	71%	44%	37%	49%
ACR70	58%	16%	24%	21%
$DAS28_{CRP}$ remission	63%	26%	27%	41%

- Well-tolerated and favourable safety profile across all doses tested
  - no meaningful effect on neutrophil count and lipid ratios
  - only infrequent abnormalities observed in laboratory assessments of liver enzymes