



Vobarilizumab, a novel best-in-class anti-IL-6R drug candidate for the treatment of rheumatoid arthritis

20 October 2016

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Rheumatoid arthritis (RA)

Treatment goals

- Remission – little or no signs and symptoms of disease
- Administration with no impact on daily life and easy to comply with
- Safe and well-tolerated



VOBARILIZUMAB: a novel anti-IL-6R drug candidate for RA

Key differentiating features

Potential benefits

Small (26kD)



Better penetration into tissues

Preferential binding to **soluble** vs membrane bound **IL-6R** (2,500 fold higher affinity to sIL-6R vs tocilizumab)

Superior efficacy/tolerability profile

Vobarilizumab (225mg every 2 weeks)

Excellent Phase IIb study results reported in July/August 2016

Combination therapy (+MTX) 24 weeks (across studies)	DAS28 _{CRP} remission	ACR 70
vobarilizumab	49%	43%
tocilizumab	32%	20%
adalimumab	23%	21%

Monotherapy 12 weeks (head-to-head study)	DAS28 _{CRP} remission	ACR 70
vobarilizumab (6 doses)	41%	21%
tocilizumab (~ 12 doses) open-label	27%	23%

tocilizumab: BREVACTA PhIII (sc) 162mg Q2W + MTX (Kivitz et al., Arthritis Care & Research, Nov 2014); note: remission is based on ESR (no CRP data available)

adalimumab: Weinblatt et al, Arthritis & Rheumatology, Sept 2015 (Phase IIb head-to-head adalimumab 40mg Q2W + MTX vs clazakizumab + MTX)



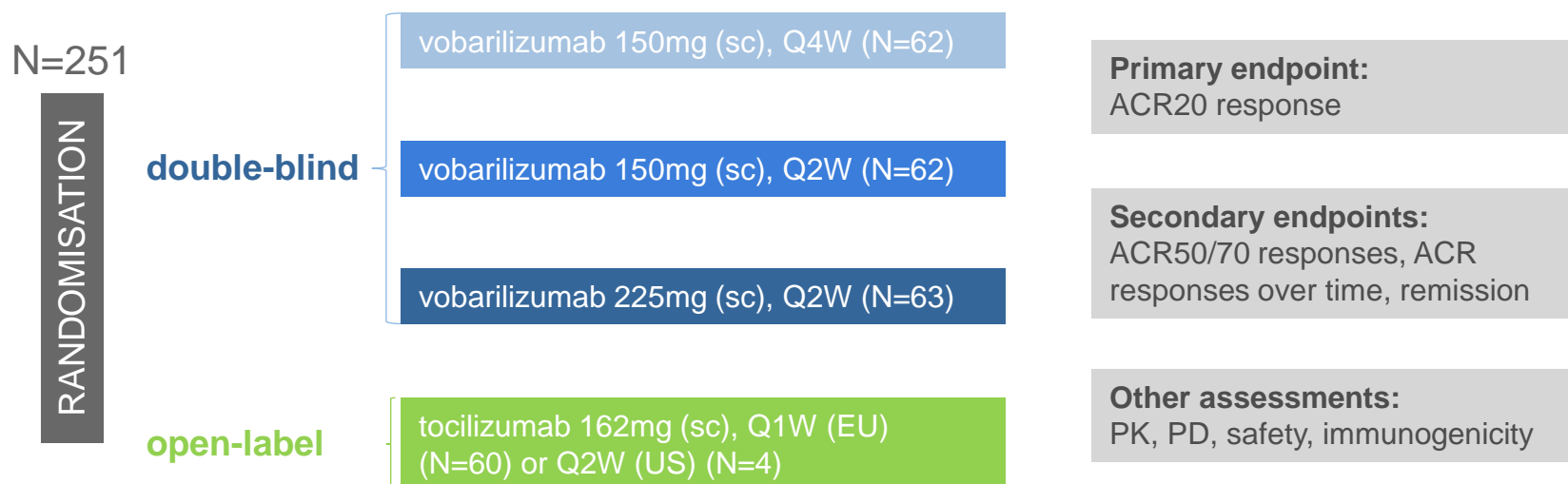
Vobarilizumab Phase IIb clinical development

Additional compelling data



12 week Phase IIb RA monotherapy study in 251 patients

- Adults with moderate to severe RA who are intolerant to MTX or for whom continued MTX is inappropriate
- 12 week study in the US, Europe, and Latin America
- Recruitment from April 2015 to February 2016

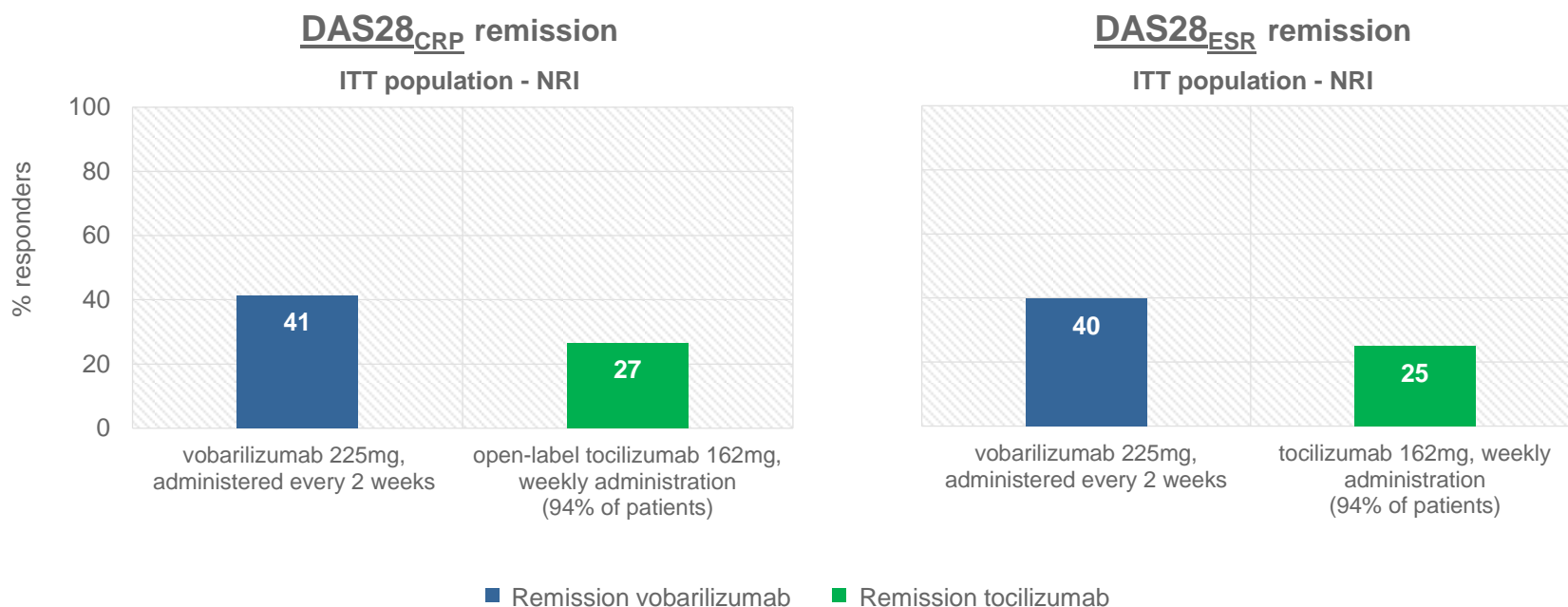


Vobarilizumab (every 2 weeks) as a monotherapy



Up to 60% more patients in clinical remission versus weekly tocilizumab

- Head-to-head Phase IIb study – responses at week 12



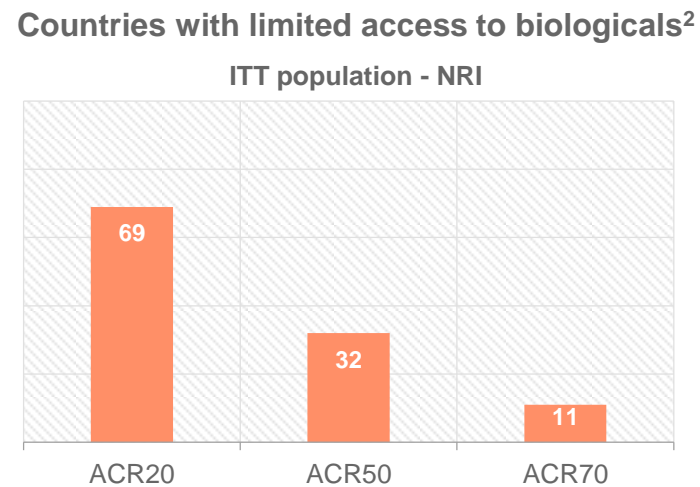
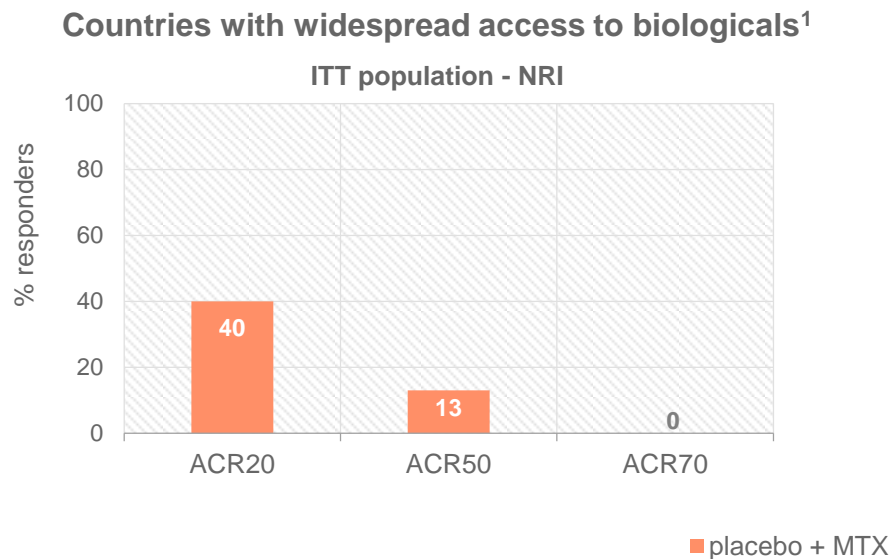
DAS28_{CRP} is a RA disease activity score based on C-reactive protein (CRP), tender and swollen joint counts of 28 defined joints and patient's global assessment of disease activity; DAS28_{ESR} is a RA disease activity score based on erythrocyte sedimentation rate, tender and swollen joint counts of 28 defined joints and patient's global assessment of disease activity. Remission: DAS28 < 2.6; low disease activity: 2.6 ≤ DAS28 ≤ 3.2

Phase IIb RA combination study with methotrexate (MTX) in 345 patients

- Adults with moderate to severe RA despite MTX therapy
- Randomised, double-blind, placebo-controlled 24 week dose ranging study in EU, USA and LATAM
- 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



Regional differences in placebo effect – ACR20/50/70 scores at week 12

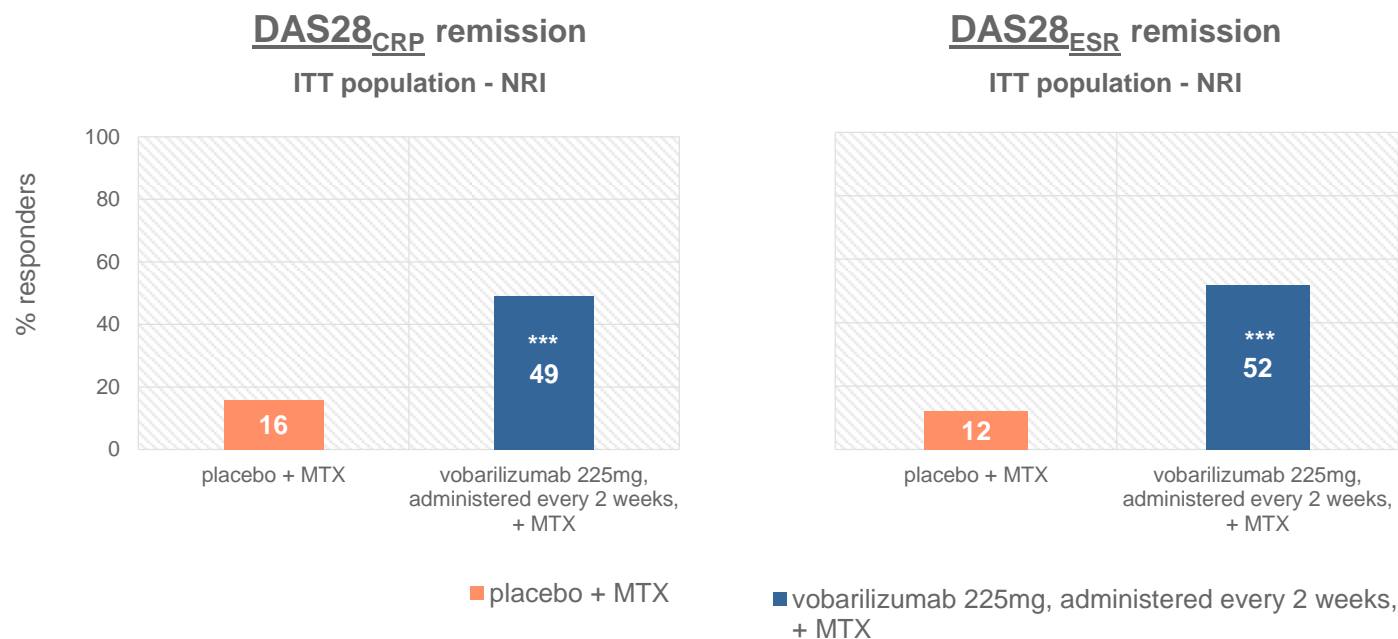


Placebo effect clearly related to trial design and location

1: Belgium, Czech Republic, Hungary, Spain, USA (vobarilizumab all doses N=62; placebo N=15)

2: Bulgaria, Georgia, Macedonia, Mexico, Poland, Republic of Moldova, Romania, Serbia (vobarilizumab all doses N=214; placebo N=54)

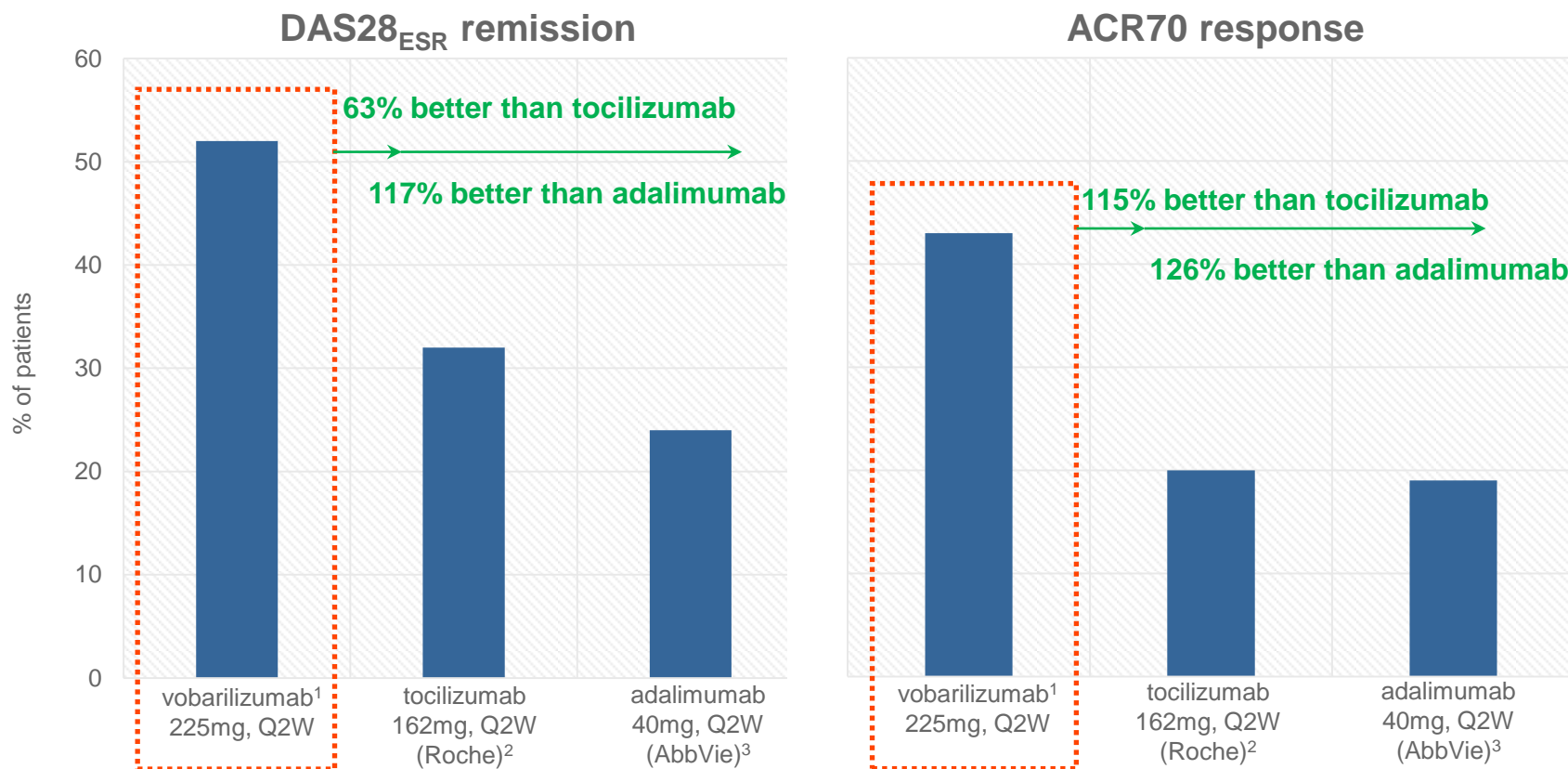
Up to 52% of patients in clinical remission at week 24



Highly statistically significant difference in remission scores versus placebo

DAS28_{CRP} is a RA disease activity score based on C-reactive protein (CRP), tender and swollen joint counts of 28 defined joints and patient's global assessment of disease activity; DAS28_{ESR} is a RA disease activity score based on erythrocyte sedimentation rate, tender and swollen joint counts of 28 defined joints and patient's global assessment of disease activity. Remission: DAS28 < 2.6; low disease activity: 2.6 ≤ DAS28 ≤ 3.2

Dramatically better efficacy* than leading commercial biologicals



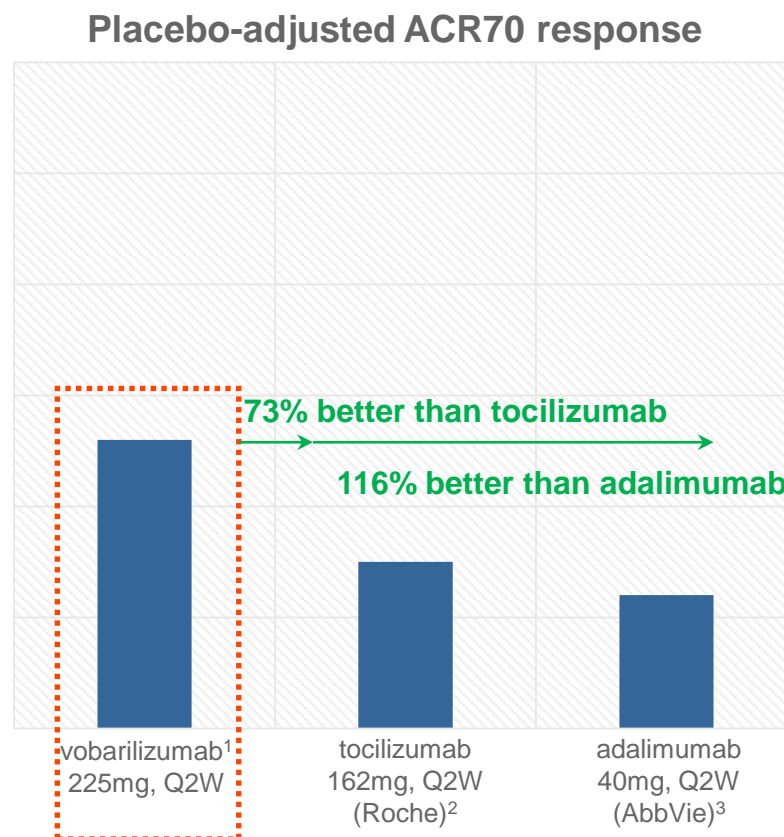
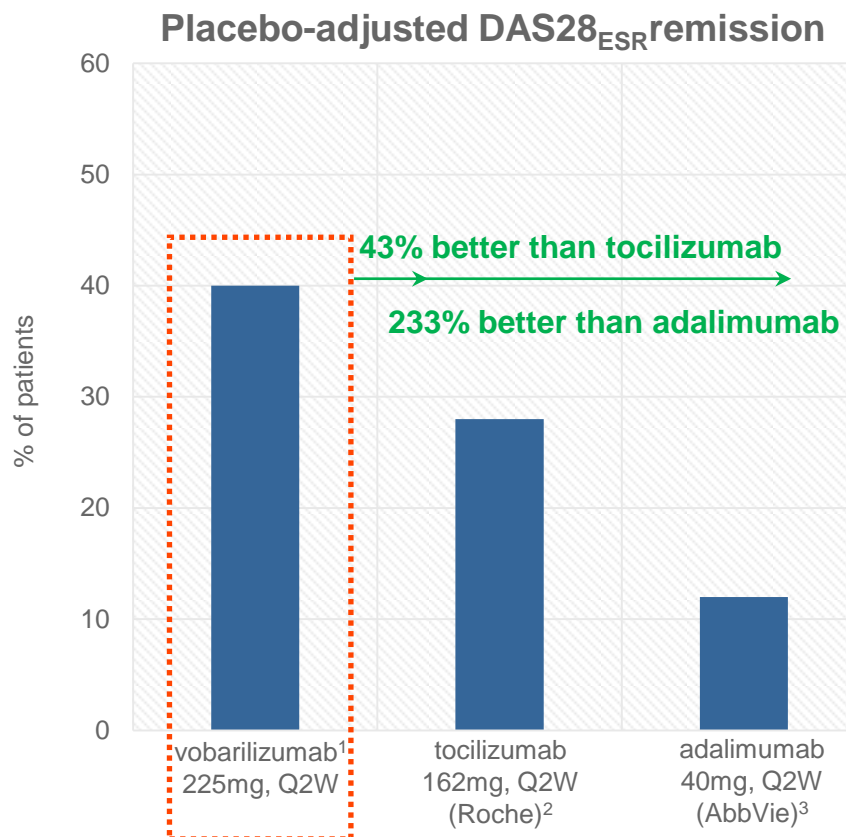
* 24-week data from combination therapy studies reported in listed publications, not resulting from head-to-head studies

¹ Phase IIb + MTX (Oct 2016); ² BREVACTA Phase III + MTX (Kivitz et al., Arthritis Care & Research, Nov 2014) ³ Phase IIb (Weinblatt et al., Arthritis & Rheumatology, Sept 2015) (note: remission based on CRP; no data on ESR available)

Vobarilizumab + MTX (placebo-adjusted scores)



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Favourable safety and immunogenicity profile

	% pts with ≥ 1 SAEs	% pts with grade 3 toxicity for neutrophils
vobarilizumab, 225mg Q2W ¹	1.4%	0.0%
tocilizumab, 162mg Q2W ²	4.6%	3.5%
adalimumab, 40mg Q2W ³	5.1%	1.9%

- Anti-vobarilizumab antibodies
 - develop in up to 31% of patients
 - BUT have no effect on PK, efficacy or safety
- Anti-adalimumab antibodies⁴
 - develop in ~30% of patients
 - AND are associated with loss of efficacy and an increased risk of adverse events
 - 1/3rd of patients become resistant to adalimumab as a result of ADAs (with a strong signal occurring early in the treatment cycle)

A Nanobody class advantage

¹ Phase IIb RA study + MTX, Ablynx August 2016; ² Kivitz et al., 2014, Arthr. Care & Res., 66, 1653-61; ³ Weinblatt et al., Arthritis Rheumatol., 67, 2591-600

⁴ Ogrič M et al., Immunol Res. July 2016; Jani M et al., Lancet Feb 2015; Schaeferbeke T, Rheumatology (Oxford) Feb 2016; Gerrit Jan Wolbink et al., J. of the Amer. Med. Ass., April 2011

Compliance of prescribed treatment regimen

Advantage of biologicals versus oral drugs

vobarilizumab Q2W	vobarilizumab Q4W	oral JAKs
26 sc doses per year	13 sc doses per year	365 oral doses per year

- Subcutaneous injections every two to four weeks are considered much easier to comply with as compared to taking a pill daily
- Based on non-compliance of oral medication in other chronic indications, one might expect compliance rates for JAKs to range from 30-80% or anything from 73-256 missed doses per year – as well as an important impact on efficacy this might have a very negative impact on sales
- We are not aware of any studies on JAKs showing the effect of non-compliance

Novel best-in-class drug candidate for the treatment of RA

- Rapid, strong and sustained effect on signs and symptoms of disease
- Much greater efficacy as a monotherapy with up to 60% more patients in clinical remission as compared to tocilizumab
- Superior effect as a combination therapy on most stringent efficacy parameters compared to leading commercial biologicals and oral anti-RA drugs in development
- Potential for monthly effective administration
- Class advantage of vobarilizumab vs antibodies demonstrated: anti-Nanobody antibodies had no effect on PK, efficacy or safety
- Superior safety profile compared to other biological anti-RA drugs

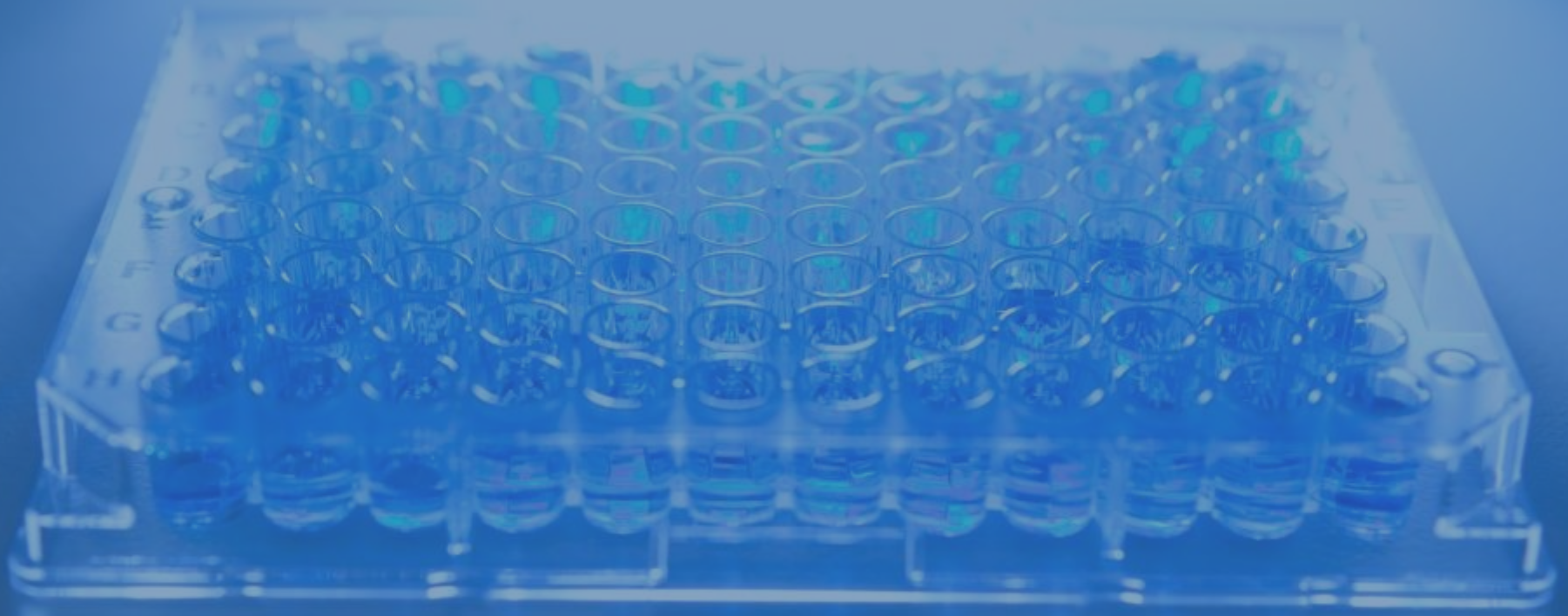
Advancing the development of vobarilizumab in RA is a top priority for Ablynx



Vobarilizumab next steps

What's next

- Phase III programme in RA
 - regulatory consultations expected in H1 2017
 - first Phase III study expected to start by end 2017
 - partnering discussions
- RA Phase II open-label extension study
 - ongoing
 - results expected in 2018
- Phase II study in 300 SLE patients
 - ongoing
 - recruitment ahead of schedule
 - results expected in H1 2018



Questions

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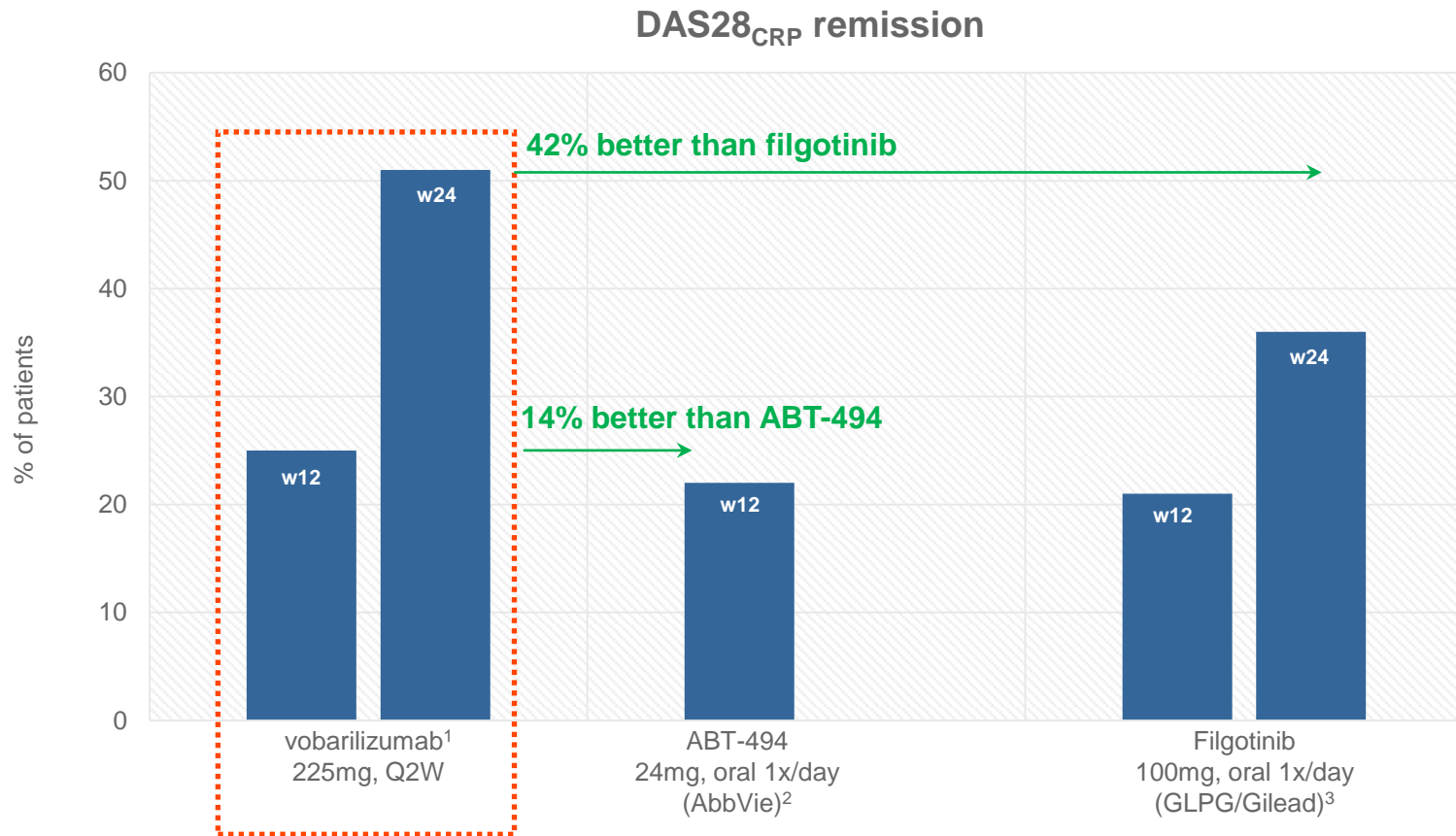
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Back-up

Superior efficacy compared to oral anti-RA drugs in development*

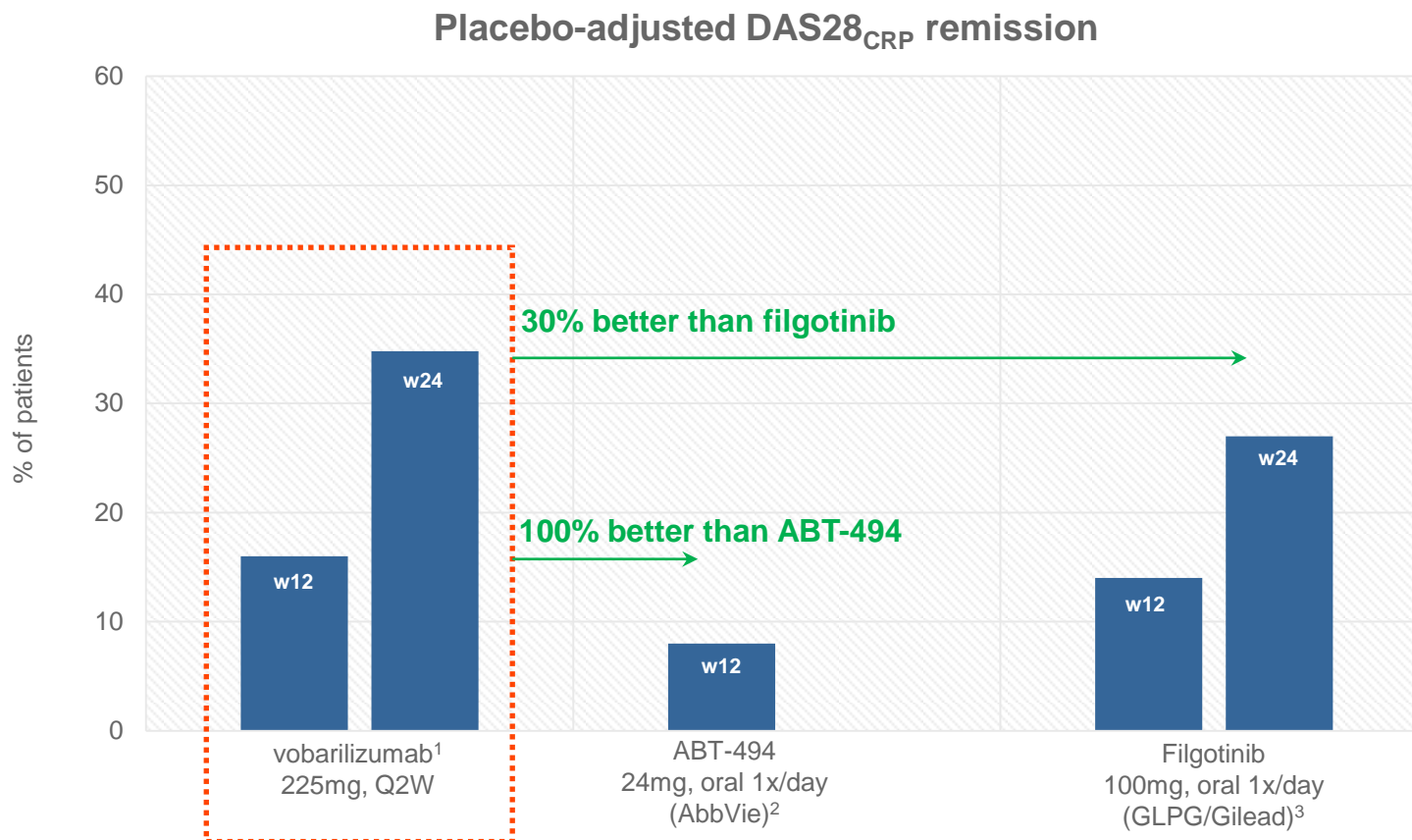


* Data reported in listed publications, not resulting from head-to-head studies

¹ Phase IIb + MTX at week 12 and 24 (August 2016; LOCF imputation); ² Phase IIb + MTX at week 12 (EULAR 2016 – NRI imputation) ³ Phase IIb + MTX (LOCF imputation) at week 12 and 24 (April 2015; July 2015)

Vobarilizumab + MTX (placebo-adjusted scores)

Superior efficacy compared to oral anti-RA drugs in development*



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