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

<table>
<thead>
<tr>
<th>Key differentiating features</th>
<th>Potential benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small (26kD)</td>
<td>Better penetration into tissues</td>
</tr>
<tr>
<td>Preferential binding to soluble vs membrane bound IL-6R (2,500 fold higher affinity to sIL-6R vs tocilizumab)</td>
<td>Superior efficacy/tolerability profile</td>
</tr>
</tbody>
</table>
Vobrilizumab (225mg every 2 weeks)

Excellent Phase IIb study results reported in July/August 2016

<table>
<thead>
<tr>
<th>Combination therapy (+MTX) 24 weeks (across studies)</th>
<th>DAS28$_{CRP}$ remission</th>
<th>ACR 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>vobarilizumab</td>
<td>49%</td>
<td>43%</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>32%</td>
<td>20%</td>
</tr>
<tr>
<td>adalimumab</td>
<td>23%</td>
<td>21%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Monotherapy 12 weeks (head-to-head study)</th>
<th>DAS28$_{CRP}$ remission</th>
<th>ACR 70</th>
</tr>
</thead>
<tbody>
<tr>
<td>vobarilizumab (6 doses)</td>
<td>41%</td>
<td>21%</td>
</tr>
<tr>
<td>tocilizumab (~ 12 doses) open-label</td>
<td>27%</td>
<td>23%</td>
</tr>
</tbody>
</table>

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
Vobarilizumab

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

**RANDOMISATION**

- **N=251**
- **double-blind**
  - Vobarilizumab 150mg (sc), Q4W (N=62)
  - Vobarilizumab 150mg (sc), Q2W (N=62)
  - Vobarilizumab 225mg (sc), Q2W (N=63)
- **open-label**
  - Tocilizumab 162mg (sc), Q1W (EU) (N=60) or Q2W (US) (N=4)

**Primary endpoint:**
- ACR20 response

**Secondary endpoints:**
- ACR50/70 responses, ACR responses over time, remission

**Other assessments:**
- PK, PD, safety, immunogenicity
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\textsubscript{CRP}** remission

\begin{tabular}{|c|c|}
\hline
\textbf{ITT population - NRI} & \\
\hline
0 & 20 & 40 & 60 & 80 & 100 \\
\hline
\text{vobarilizumab 225mg, administered every 2 weeks} & 41 \\
\text{open-label tocilizumab 162mg, weekly administration (94\% of patients)} & 27 \\
\hline
\end{tabular}

**DAS28\textsubscript{ESR}** remission

\begin{tabular}{|c|c|}
\hline
\textbf{ITT population - NRI} & \\
\hline
0 & 20 & 40 & 60 & 80 & 100 \\
\hline
\text{vobarilizumab 225mg, administered every 2 weeks} & 40 \\
\text{tocilizumab 162mg, weekly administration (94\% of patients)} & 25 \\
\hline
\end{tabular}

\textbf{Remission vobarilizumab}  \hspace{1cm} \textbf{Remission tocilizumab}

DAS28\textsubscript{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\textsubscript{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: $2.6 \leq \text{DAS28} \leq 3.2$

\text{ITT = intent-to-treat} \hspace{1cm} \text{NRI: non-responder imputation}
**Vobarilizumab**

**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

**Randomisation**

\[ 1:1:1:1:1 \]

N=345

- Placebo + MTX (sc) (N=69)
- Vobarilizumab 75mg, Q4W (sc) + MTX (N=69)
- Vobarilizumab 150mg, Q4W (sc) + MTX (N=70)
- Vobarilizumab 150mg, Q2W (sc) + MTX (N=68)
- Vobarilizumab 225mg, Q2W (sc) + MTX (N=69)

**Primary endpoint:** ACR20 response

**Secondary endpoints:**
- ACR50/70 responses
- ACR responses over time, remission

**Other assessments:**
- PK, PD, safety, immunogenicity

MTX = methotrexate  
sc = subcutaneous injection
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)

ITT = intent-to-treat  NRI: non-responder imputation
**Vobarilizumab + MTX**

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

![Graph showing DAS28\textsubscript{CRP} and DAS28\textsubscript{ESR} remission](image)

- **DAS28\textsubscript{CRP} remission**
  - ITT population - NRI
  - % responders: 16 vs 49
  - *p* < 0.001 vs placebo

- **DAS28\textsubscript{ESR} remission**
  - ITT population - NRI
  - % responders: 12 vs 52
  - *p* < 0.001 vs placebo

Highly statistically significant difference in remission scores versus placebo

DAS28\textsubscript{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\textsubscript{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

**ITT = intent-to-treat**

**NRI: non-responder imputation**
Vobarilizumab + MTX

Dramatically better efficacy* than leading commercial biologicals

DAS28_{ESR} remission

- 63% better than tocilizumab
- 117% better than adalimumab

ACR70 response

- 115% better than tocilizumab
- 126% better than adalimumab

*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)

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 (August 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

Favourable safety and immunogenicity profile

<table>
<thead>
<tr>
<th></th>
<th>% pts with ≥ 1 SAEs</th>
<th>% pts with grade 3 toxicity for neutrophils</th>
</tr>
</thead>
<tbody>
<tr>
<td>vobarilizumab, 225mg Q2W¹</td>
<td>1.4%</td>
<td>0.0%</td>
</tr>
<tr>
<td>tocilizumab, 162mg Q2W²</td>
<td>4.6%</td>
<td>3.5%</td>
</tr>
<tr>
<td>adalimumab, 40mg Q2W³</td>
<td>5.1%</td>
<td>1.9%</td>
</tr>
</tbody>
</table>

• 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)

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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
Compliance of prescribed treatment regimen

Advantage of biologicals versus oral drugs

<table>
<thead>
<tr>
<th>vobarilizumab Q2W</th>
<th>vobarilizumab Q4W</th>
<th>oral JAKs</th>
</tr>
</thead>
<tbody>
<tr>
<td>26 sc doses per year</td>
<td>13 sc doses per year</td>
<td>365 oral doses per year</td>
</tr>
</tbody>
</table>

- 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

Vangeli et al., Adv. Ther., Nov 2015
Vobarilizumab

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

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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Back-up
Superior efficacy compared to oral anti-RA drugs in development*
Vobarilizumab + MTX (placebo-adjusted scores)

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

Placebo-adjusted DAS28\textsubscript{CRP} remission

* 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); 3 Phase IIb + MTX (LOCF imputation) at week 12 and 24 (April 2015; July 2015)