Remission Induction with Etanercept Plus Methotrexate in Early Moderate-to-Severe RA: The PRIZE Study (Phase 1)

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Background

- Currently, the target outcome for early rheumatoid arthritis (RA) therapy is clinical remission1-3
- COMET, a previous study of etanercept (ETN) plus methotrexate (MTX) therapy in patients with early rheumatoid arthritis (≤2 years from diagnosis), showed high clinical remission rates1
- It is unknown whether remission achieved with ETN + MTX can be maintained with dose reduction/withdrawal of etanercept/no drug
- Phase 1 of the on-going PRIZE1 trial evaluated induction of Disease Activity Score (28-joint count, DAS28) erythrocyte sedimentation rate (ESR) remission in patients with early active moderate-to-severe RA (symptoms ≤12 months) treated with ETN 50 mg QW plus MTX

Study Design: Overview of Phases 1-3

Randomize responders achieving DAS28 ≤2.6 at Week 26 and/or DAS28 ≤3.2 at Week 52

Early moderate-to-severe RA patients ETN 50mg QW/MTX (10-25 mg QW)

Week 4 8 12 16 20 24

ETN 25 mg QW + MTX Drug free
PL injection + MTX Drug free
PL injections + PL capsules Drug free

Phase 1: Open label
Phase 2: Double blind
Phase 3: Dose tapering for 2-4 weeks, then observation

Study Design and Measures: Phase 1 Open Label

Inclusion Criteria
- RA symptom onset ≤12 months from enrollment
- DAS28 >3.2
- MTX and biologic naive

Responses
- DAS28 ≤2.6 at Weeks 26 and 52
- MTX and biologic naive

Non-Responders (DAS28 >3.2) were active in the study

Non-Responders (DAS28 >2.6) were taken into Phase 2

- The dose of MTX was optimized by 5 mg/week from 10 mg/week to a maximum of 25 mg/week (mean 16.4 mg)
- Corticosteroid boost given to patients with DAS28>3.2 at Weeks 13 and/or 26

Disclosures

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References

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Phase 1 Main Endpoints

- DAS28 low disease activity (LDA, ≤3.2) and remission (<2.6)
- ACR/EULAR remission criteria
- ACR criteria for improvements in response
- Simplified Disease Activity Index (SDAI)
- Clinical Disease Activity Index (CDAI)
- Complete response, defined as:
  - DAS28 ≤2.6
  - Health Assessment Questionnaire (HAQ) ≤0.5
  - No radiographic progression over 52 weeks
- Modified Total Sharp Score (mTSS)

(1) DAS28 low disease activity (LDA, ≤3.2) and remission (<2.6)
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(5) Clinical Disease Activity Index (CDAI)
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Statistical Considerations

- Sample size: Planned to enrol 300 subjects in Phase 1 to ensure the randomization of 165 into Phase 2 after 52 weeks.
- Analysis population definitions:
  - Modified intention-to-treat (mITT): all subjects who received treatment and had clinical data.
  - Radiographic ITT: all mITT subjects with valid baseline and follow-up x-rays.
- Phase 1 analyses: descriptive statistics.
- Statistical comparisons to baseline were made using paired t-tests.
- Observed case (OC) analysis is defined as all subjects with data at that time point.
- Last observation carried forward (LOCF) analysis is shown only at Week 52.

Baseline Demographic Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline Mean</th>
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</thead>
<tbody>
<tr>
<td>n=306</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>49.9 (13.7)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>213 (69.6)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>286 (93.5)</td>
</tr>
<tr>
<td>Black</td>
<td>3 (1.0)</td>
</tr>
<tr>
<td>Asian</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (2.9)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>26.1 (5.2)</td>
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<tr>
<td>Female</td>
<td>25.7 (5.0)</td>
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</tbody>
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Baseline and Week 52 Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Baseline Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCP3 antibody, n (%) (+ve/missing)</td>
<td>189 (61.8)/1 (0.3)</td>
</tr>
<tr>
<td>Rheumatoid factor, n (%) (+ve/missing)</td>
<td>167 (55.5)/1 (0.3)</td>
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<tr>
<td>SJC28</td>
<td>6.0 (3.9)</td>
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<tr>
<td>TJC28</td>
<td>10.0 (6.4)</td>
</tr>
<tr>
<td>Tender/swollen joint count - 28 joints</td>
<td>14.1 (7.3)/3.2 (1.6)</td>
</tr>
<tr>
<td>Patient global assessment score</td>
<td>58.9 (23.6)</td>
</tr>
<tr>
<td>SDAI</td>
<td>38.3 (14.0)</td>
</tr>
<tr>
<td>HAQ DI</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>mTSS</td>
<td>7.9 (12.7)</td>
</tr>
<tr>
<td>ΔmTSS &lt;0.5, n (%)</td>
<td>163 (81.6)</td>
</tr>
</tbody>
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Proportion of Patients Achieving LDA, Remission, and Complete Response

Proportions achieved are similar when comparing mITT to rITT analysis.

Change in DAS28 Over 52 Weeks: Observed Cases (Completers)

All values P<0.0001 vs. baseline, 95% CI.
Conclusions
- Patients showed significant and rapid improvement in disease activity and function with combined 50 mg ETN (QW) and MTX therapy in Phase 1 of the PRIZE trial
- By Week 26 half of observed cases achieved DAS28 remission, reaching 89% at Week 52 (71% LOCF)
- 66% of observed cases achieved ACR/EULAR Boolean remission at week 52 (52% LOCF)
- Only 18% of completers (19% LOCF) had increases in mean mTSS of >0.5
- There were no unexpected safety or tolerability findings
- 64.7% of enrolled patients qualified for the next phase of the trial, in which treatment will be reduced and/or withdrawn

Safety Evaluation
- There were no unexpected safety or tolerability findings throughout the study period – safety results were similar to previous studies with ETN and MTX
- The most common treatment-emergent adverse events (AEs), occurring in ≤5% of patients, were nausea (12.7%) and nasopharyngitis (12.7%)
- Serious adverse events (SAEs) were reported for 9.2% of patients (n=28). No deaths were reported in Phase 1 of the study
- Seven patients (2.3%) reported SAEs that were investigator-identified infections: eroding gastritis, abscess, bronchitis, empyema, infected cyst, lower respiratory tract infection viral, pneumonia, and soft tissue infection
- One event (0.3%) of opportunistic infection (herpes zoster) was reported and there were no cases of tuberculosis
- Two patients (0.7%) reported three malignancies (ovarian cancer, uterine cancer, prostate cancer)

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- We wish to thank all patients who participated in the trial and all investigators and medical staff of the participating centers