ABACETEPT TREATMENT FOR PATIENTS WITH EARLY ACTIVE PRIMARY SJÖGREN’S SYNDROME: OPEN-LABEL EXTENSION PHASE OF A RANDOMIZED CONTROLLED PHASE III TRIAL


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Background: Abacetape (CTLA-4-Ig) targets the CD80/CD86:CD28 co-stimulatory pathway required for full T-cell activation and T-cell dependent activation of B-cells. The Abacetape Sjögren Active Patients phase III (ASAPIII) trial is a mono-center, investigator-initiated, placebo controlled study with an open-label extension phase (NCT02067910), which assessed the efficacy and safety of weekly subcutaneous abatacept (125mg) in patients with early active primary Sjögren’s syndrome (pSS). Previous analyses of the double blind phase showed no significant effect of abatacept treatment compared to placebo on the primary endpoint, difference in EULAR Sjögren’s syndrome disease activity index (ESSDAI) at week 24.1

Objectives: To evaluate the efficacy and safety of extended (48 weeks) open label abatacept treatment in pSS patients.

Methods: Included patients had biopsy-proven pSS, fulfilled the AECG and ACR-EULAR criteria, had disease duration ≤7 years (median 2 years), ESSDAI ≥5, and 89% were anti-SSA positive. All 40 patients who received abatacept (ABA) in week 0-24 were subsequently treated with abatacept from week 24-48. Of the 40 patients who received placebo (PLB) in week 0-24, 2 were lost to follow up, and 38 were treated with abatacept from week 24-48. Systemic disease activity (ESSDAI), patient reported symptoms (ESSPRI), serological outcomes (RF and IgG), ocular staining score (OSS) and unstimulated whole saliva flow (UWS) were assessed. We evaluated whether outcomes improved within treatment groups, from week 0 to subsequent visits and from week 24 to subsequent visits:

1. Within ABA ➔ ABA treated patients:
   a. Week 0-48 to assess overall efficacy.
   b. Week 24-48 to assess additional efficacy of long term treatment.
2. Within PLB ➔ ABA treated patients:
   a. Week 0-24 to assess whether a placebo effect occurred.
   b. Week 24-48 to assess short-term efficacy of open label ABA.

GEE modeling was used to test significance of changes over time. Missing data to abatacept. Biological activity was decreased by abatacept treatment. 48-week abatacept treatment improved OSS, and might improve UWS. Abatacept was well tolerated by pSS patients.

References:
[1] van Nijmegen et al. Lancet Rheumatol. Published online 31-01-2020

RESULTS:
GEE modeling was used to test significance of changes over time. Missing data...
end-stage kidney disease (ESKD). The target of therapy is complete response (proteinuria <0.5-0.7g/24h with [near-]normal glomerular filtration rate) by 12 months, but this can be extended in patients with baseline nephrotic-range proteinuria. Hydroxychloroquine is recommended for regular ophthalmologic monitoring. In active proliferative LN, initial (induction) treatment with mycophenolate mofetil (MMF 2-3g/day, or mycophenolic acid at equivalent dose) or low-dose intravenous cyclophosphamide (CY; 500mg x6 biweekly doses), both combined with glucocorticoids (pulses of intravenous methylprednisolone, then oral prednisone 0.3-0.5mg/kg/day) is recommended. MMF/CNI (especially tacrolimus) combination and high-dose CY are alternatives, for patients with nephrotic-range proteinuria and adverse prognostic factors. Subsequent long-term maintenance treatment with MMF or azathioprine should follow, with no or low-dose (<7.5mg/day) glucocorticoids. The choice of agent depends on the initial regimen and plans for pregnancy. In non-responding disease, switch of induction regimens or rituximab are recommended. In pure membranous LN with nephrotic-range proteinuria or proteinuria >1g/24h despite renin-angiotensin-siraldosterone blockade, MMF in combination with glucocorticoids is preferred. Assessment for kidney and extra-renal disease activity, and management of comorbidities is lifelong with repeat kidney biopsy in cases of incomplete response or nephritic flares. In ESKD, transplantation is the preferred kidney replacement option with immunosuppression guided by transplant protocols and/or extra-renal manifestations.

**Conclusion:** The updated recommendations intend to inform rheumatologists, nephrologists, patients, national professional societies, hospital officials, social security agencies and regulators about the treatment of LN based on most recent evidence.

**Disclosure of Interests:** Antonios Fanouriakis Paid instructor for: Paid instructor for for Enorasis, Amirouche A. Benkhedda Speakers bureau: Paid speaker for Roche, Genesio Pharma, Mylan, Myro Kostopouloou: None declared, Kim Cheema: None declared, Hans-Joachim Andors: None declared, Martin Aringer Consultant of: Boehringer Ingelheim, Roche, Speakers bureau: Boehringer Ingelheim, Roche, Ingeborg Bajema Consultant of: GSK, John N. Boletis Grant/research support from: GSK, Pfizer, Pfzer for: GSK, Abbvie, UCN, Enorasis, Elior Frangou: None declared, Frederic Houssiau Grant/research support from: Consultant of: GSK, Jane Hollls: None declared, Alexandre Karrai: None declared, Francesca Marchioni: None declared, Stephen Marks: None declared, Gabriela Moroni: None declared, Marta Mosca: None declared, Ioannis Pardis: None declared, Manuel Praga: None declared, Matthias Schneider Consultant of: Abbvie, AstraZeneca, Celgene, Celltrion, Chugai, Eli Lilly, Gilead, ILTOO, Janssen, Novartis-Sandoz, Pfizer Inc, Sanofi, Amin, Sano, Sanofi, Consultant of: Abbvie, AstraZeneca, Celgene, Celltrion, Chugai, Eli Lilly, Gilead, ILTOO, Janssen, Novartis-Sandoz, Pfizer Inc, Sanofi, Amin, Vladimir Tesar: None declared, Maria Trachana: None declared, Ronald van Volkenhoven Consultant of: Consultant of: Abbvie, Mycophenolate mofetil (MMF), or low-dose intravenous cyclophosphamide (CY; 500mg x6 biweekly doses), vs. placebo with or without rituximab.

**Results:** Overall, 448 pts were randomised (efficacy: 223/group; safety: 224/group). Significantly more BEL (43%) than PBO (32.3%) pts achieved PERR at Wk 104 (OR 1.55, 95% CI 1.04, 2.32; p=0.0311). More BEL than PBO pts achieved key secondary and other efficacy endpoints (Table). Overall, 214 (95.5%) BEL and 211 (94.2%) PBO pts had ≥1 adverse event (AE); 58 (25.9%) BEL and 67 (29.9%) PBO pts had ≥1 serious AE; 29 (12.9%) pts in each group had ≥1 AE resulting in study treatment discontinuation; 4 (1.8%) BEL and 3 (1.3%) PBO pts developed on-treatment fatal AEs.

**Conclusion:** In the largest LN study to date, data from BLISS-LN demonstrate that BEL plus ST significantly improves LN renal responses compared with ST alone with a favourable safety profile.

**Study funding:** GSK.

**Table.**

<table>
<thead>
<tr>
<th>Endpoint, n (%)</th>
<th>PBO (n=223)</th>
<th>BEL (n=223)</th>
<th>OR/HR (95% CI) p-value vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRR at Wk 104*</td>
<td>44 (19.7)</td>
<td>67 (30.0)</td>
<td>OR 1.74 (1.11, 2.74) p=0.0167</td>
</tr>
<tr>
<td>PERR at Wk 52*</td>
<td>79 (35.4)</td>
<td>104 (46.6)</td>
<td>OR 1.59 (1.06, 2.38) p=0.0245</td>
</tr>
<tr>
<td>Time to PERR through Wk 104</td>
<td>72 (32.3)</td>
<td>93 (40.3)</td>
<td>HR 1.46 (0.96, 2.23) p=0.0189</td>
</tr>
<tr>
<td>Wk 104†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to CRR through Wk 104</td>
<td>44 (19.7)</td>
<td>67 (30.0)</td>
<td>HR 1.58 (1.08, 2.31) p=0.041</td>
</tr>
<tr>
<td>Time to renal-related event or death†</td>
<td>63 (28.3)</td>
<td>35 (15.7)</td>
<td>HR 0.51 (0.34, 0.77) p=0.0014</td>
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<tr>
<td>SLEDAI-S2K score &lt;4 points at Wk 104*</td>
<td>41 (18.4)</td>
<td>62 (27.8)</td>
<td>OR 1.76 (1.11, 2.78) p=0.0164</td>
</tr>
</tbody>
</table>

*PBO and BEL columns represent the n (%) responders

1 Data presented as n (% cumulative incidence)


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