Tofacitinib (CP-690,550) in combination with traditional disease-modifying anti-rheumatic drugs: patient-reported outcomes from a Phase 3 study in patients with active rheumatoid arthritis and an inadequate response to disease-modifying anti-rheumatic drugs

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Disclosures
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Evidence-based Medicine
- Three key references for this study are
  - V Strand and J Singh. Newer biological agents: impact on health-related quality of life and productivity. Drugs 2010; 70 (2); 121-145

Introduction
- Tofacitinib (CP-690,550) is a novel oral JAK inhibitor that is being investigated as a targeted immunomodulator and disease-modifying therapy for RA.1,2
- 1st Phase 3 (ORAL Solo) monotherapy presented at ACR 20103
- ORAL Sync: Phase 3 RCT of tofacitinib in combination with non-biologic DMARDs in adult DMARD-IR patients with active RA
  - Tofacitinib 5 and 10 mg BID demonstrated rapid, significant and clinically meaningful reductions in signs and symptoms of RA, and physical function
  - No new safety signals detected, presented at EULAR 20114
- Here we present patient-reported outcomes from this Phase 3 RCT

3 Fleischmann et al. ACR 2010; 4 Kremer et al. EULAR 2011
ORAL Sync: Study Design

- End of placebo control
- Double-blind, placebo-controlled period
  - 5 mg BID (n=315)
  - 10 mg BID (n=318)
  - Placebo (n=79)
  - Placebo (n=80)
- Double-blind, active extension period
  - 5 mg BID (n=315)
  - 10 mg BID (n=318)
  - Placebo (n=79)
  - Placebo (n=80)

- Patients randomized at baseline to one of four sequences (4:4:1:1)
- At Month 3, all ‘non-responder’ (<20% reduction from baseline in SJC/TJC) placebo patients blindly advanced to tofacitinib 5 mg (n=38) or 10 mg BID (n=40)
- At Month 6, all remaining placebo patients were blindly advanced to active therapy

ORAL Sync: Endpoints

- Primary outcome measures – vs placebo
  - ACR20 response rate at Month 6
  - HAQ-DI mean change from baseline at Month 3
  - DAS28-4(ESR) <2.6 response rate at Month 6
  - Safety and tolerability
- Mean changes from baseline in patient-reported outcomes at Month 3
  - HAQ-DI; a co-primary endpoint
  - Patient Global Assessment of Disease Activity (PtGA)
  - Pain (VAS scale)
  - Short-Form 36
  - FACIT-Fatigue Scale
  - MOS Sleep Scale
- Statistical significance based on nominal p-value <0.05, with no multiple comparisons correction (full analysis set, observed data)

ORAL Sync: Inclusion and Exclusion Criteria

- Key inclusion criteria
  - Diagnosis of RA for ≥6 months by ACR criteria
  - Active disease (≥4 tender and swollen joints)
  - ESR >28 mm/h or CRP >7 mg/L
  - Prior inadequate response to ≥1 DMARD
  - Patients remain on ≥1 background traditional DMARD
- Key exclusion criteria
  - Cytopenias
  - Estimated GFR ≤40 mL/min (Cockcroft-Gault calculation)
  - Total AST or ALT >1.5 x ULN
  - Evidence of active infection, including latent or active TB infection

ORAL Sync: Patient Demography

<table>
<thead>
<tr>
<th>Region of origin and % patients per group in each region</th>
<th>5 mg BID (n=315)</th>
<th>10 mg BID (n=318)</th>
<th>PBO (n=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>22.0</td>
<td>19.6</td>
<td>22.8</td>
</tr>
<tr>
<td>South America</td>
<td>8.3</td>
<td>10.0</td>
<td>8.2</td>
</tr>
<tr>
<td>Europe</td>
<td>28.3</td>
<td>29.3</td>
<td>26.1</td>
</tr>
<tr>
<td>Rest of World</td>
<td>41.4</td>
<td>41.1</td>
<td>44.9</td>
</tr>
</tbody>
</table>

*28.3% of patients were from China (67.3% of Rest of World patients)
Mean BL value [range]      5 mg BID n=315  10 mg BID n=318  PBO n=159
DAS28-4(ESR), mean          6.29   6.36   6.30
HAQ-DI [0–3]                1.44   1.43   1.35
PtGA [0–100]                59.03  60.22  57.92
VAS pain [0–100]            57.08  58.28  57.11
SF-36 PCS [0–100]           32.44  32.02  32.74
SF-36 MCS [0–100]           40.86  41.56  41.67
FACIT-F [0–52]              29.01  28.65  29.72
MOS Sleep Scale [12–71]     41.05  40.89  39.75

ORAL Sync: PtGA and Pain at Month 3

PBO       Tofacitinib 5 mg BID       Tofacitinib 10 mg BID
PtGA      BL values                  57.92  59.03  60.22
          LSM ∆ from BL                -12.54 -24.82 -28.19
          MCID                        ***  ***  ***
          P-values                   ***  ***  ***

Pain      BL values                  57.11  57.08  58.58
          LSM ∆ from BL                -11.38 -24.18 -26.78
          MCID                        ***  ***  ***
          P-values                   ***  ***  ***

Statistically significant decreases from BL in PtGA and Pain vs PBO
**p<0.0001 vs PBO

ORAL Sync: HAQ-DI Response Rate at Month 3

BL values  1.35  1.44  1.43
          LSM ∆ from BL                -0.21  -0.46  -0.56
          MCID                        ***  ***  ***
          P-values                   ***  ***  ***

Statistically significantly decreases from BL vs PBO
**p<0.0001 vs PBO

ORAL Sync: SF-36 Physical and Mental Component Scores at Month 3

Physical component score

BL values  32.73  32.44  32.02
          LSM ∆ from BL                2.40  5.92  7.54
          MCID                        ***  ***  ***
          P-values                   ***  ***  ***

Mental component score

BL values  41.67  40.86  41.56
          LSM ∆ from BL                1.63  4.39  4.40
          MCID                        ***  ***  ***
          P-values                   ***  ***  ***

Statistically significant changes from BL in SF-36 PCS and MCS vs PBO
*p<0.05; **p<0.0001 vs PBO
ORAL Sync: SF-36 Domain Scores at Month 3

- Physical functioning
- Role physical
- Bodily pain
- Role emotional
- General health
- Vitality
- Social functioning

AGNorms 10mg-Month3 (n=291) 10mg-Month3 (n=294) Placebo-Month0 (n=147) Composite (Wt) Baseline

*p<0.05; **p<0.01; ***p<0.0001 vs PBO

ORAL Sync: Fatigue and Sleep at Month 3

- FACIT-F
- MOS Sleep Scale

FACIT-F from BL

MOS Sleep Scale

**p<0.01; ***p<0.0001 vs PBO

ORAL Sync: % of Patients Reporting Improvements ≥MCID at Month 3

- VAS pain
- PtGA
- HAQ-DI
- SF-36 PCS

**p<0.01; ***p<0.0001 vs PBO; NNT, number needed to treat

ORAL Sync: Conclusions at Month 3

- Tofacitinib (5 and 10 mg BID) treatment resulted in consistent statistically significant improvements vs PBO in:
  - HAQ-DI (co-primary endpoint)
  - PtGA
  - Pain (VAS)
  - SF-36 physical and mental component scores
  - 7 of 8 domains in 5 mg and all 8 domains of SF-36 in 10 mg, respectively
  - Fatigue (FACIT-F)
  - Sleep (MOS Sleep Scale)

- These were clinically meaningful in HAQ-DI, PtGA, Pain, SF-36 PCS and MCS scores: 65–69% and 70–74% patients reported changes ≥MCID in 5 and 10 mg BID groups, respectively

- NNT ranged from 4.6–5.8 (5 mg) and 3.7–4.3 (10 mg)

- Maintenance of benefit by these endpoints was observed at Month 6
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### Questions