Dapagliflozin Added To Verinurad Plus Febuxostat Reduces Serum Uric Acid levels Without Increasing Urinary Uric Acid Excretion In Subjects With Hyperuricemia: The QUARTZ Study

Stack AG,1 Erdlandson F,1 Han D,2 Oscarsson J,1 Goldwater R,1 Dronamraju N,3 Johansson S,4 Johnson E1

1University of Gothenburg, Gothenburg University Medical School; 2University of Lørensen, Lørensen, Iceland; 3AstraZeneca R&D, Gottingen, Sweden; and 4Gothenburg, BI, USA. PAREXEL International, Calabasas, USA; PAREXEL International,2315 International, Cedar, USA; PAREXEL International, Baltimore, USA.

Background
- Hyperuricemia is associated with gout, kidney stones and CV events.1,2
- Lowering serum uric acid confers clinical benefits but excessive urinary excretion of uric acid may damage renal tubules due to crystallization.3,4
- Verinurad (URAT1 inhibitor) added to febuxostat (xanthine oxidase inhibitor) reduces serum uric acid without increasing baseline uric acid excretion.
- Dapagliflozin (SGLT2 inhibitor) reduces serum uric acid by an unclear mechanism.5,6 and information is lacking on uric acid excretion when dapagliflozin is added to a verinurad + febuxostat combination.
- We evaluated effects of dapagliflozin, on top of verinurad + febuxostat, on serum uric acid and urinary uric acid excretion in hyperuricemic subjects.

Objectives
- To explore the effects of dapagliflozin on urinary uric acid excretion and markers of renal function when combined with verinurad + febuxostat.
- To assess the pharmacokinetics of verinurad, febuxostat and dapagliflozin.

Methods
- Randomized, phase 2, placebo-controlled, 2-way crossover design study
- Subjects (n=36) with asymptomatic hyperuricemia were randomized (1:1) to each of two treatments (Figure 1):
  - Oral once daily verinurad 9mg + febuxostat 80mg + dapagliflozin 10mg
  - Oral once daily verinurad 9mg + febuxostat 80mg + placebo

Results
- Subject disposition and characteristics
  - All subjects had hyperuricemia but were otherwise healthy and completed at least 1 treatment period; 35 subjects completed the study and 1 discontinued due to protocol deviation.
  - Baseline characteristics are shown in Table 1.

Conclusions
- Addition of dapagliflozin to verinurad + febuxostat in healthy subjects with hyperuricemia significantly reduces serum uric acid concentration.
- Peak uric acid excretion is not significantly affected by dapagliflozin when added to verinurad + febuxostat at the tested doses.
- These findings suggest that dapagliflozin can be safely combined with verinurad + febuxostat without adversely affecting kidney function.

Reference
3. Fathallah 4. Austin Stack provides consultancy to AstraZeneca, Gruenenthal, and Menarini. David Han is an employee of California Clinical Trial Medical Group in affiliation with PAREXEL. Ronald Goldwater is an employee of PAREXEL. Fredrick Erlandsson, Jan Oscarsson, Nalina Dronamarju, Susanne Johansson, and Eva Johnsson are employees of AstraZeneca.

Table 1

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Verinurad + febuxostat</th>
<th>Verinurad + febuxostat + dapagliflozin</th>
<th>Verinurad + febuxostat + placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>42.3 (12.0)</td>
<td>42.3 (12.0)</td>
<td>42.3 (12.0)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>35 (97.2)</td>
<td>35 (97.2)</td>
<td>35 (97.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Black 17 (47.2)</td>
<td>17 (47.2)</td>
<td>17 (47.2)</td>
</tr>
<tr>
<td></td>
<td>White 14 (38.9)</td>
<td>14 (38.9)</td>
<td>14 (38.9)</td>
</tr>
<tr>
<td></td>
<td>Other 5 (13.9)</td>
<td>5 (13.9)</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Serum uric acid, µmol/L, mean (SD)</td>
<td>94.4 (14.2) / 95.5 (14.4)</td>
<td>94.4 (14.2) / 95.5 (14.4)</td>
<td>94.4 (14.2) / 95.5 (14.4)</td>
</tr>
<tr>
<td>Serum creatinine, µmol/L, mean (SD)</td>
<td>84.5 (14.7) / 82.841</td>
<td>84.5 (14.7) / 82.841</td>
<td>84.5 (14.7) / 82.841</td>
</tr>
</tbody>
</table>

Figure 1. Study design (NCT03316131)

Mean serum uric acid difference for verinurad + febuxostat + placebo = 62.309 (95% CI: 4.984, 119.634).

Figure 2. Comparison of peak urinary uric acid excretion rates

- Mean (SD) change from baseline in uric acid excretion rate over 24 h on Day 7 was similar between groups (Figure 3A).
- Subjects receiving dapagliflozin showed significantly reduced serum uric acid on Day 7 versus Day -1 (LSM difference –62.31 µmol/L, 95% CI: –82.841, –41.778) (Figure 3B).

Figure 3A. Comparison of hourly urinary uric acid excretion rate over 24 h (mean changes from baseline at Day 7)

Figure 3B. Difference in serum uric acid concentrations (Day 7)

- Addition of dapagliflozin had no significant effect on the excreted amounts of creatinine, cystatin-C, or sodium over 24 h
- Peak plasma levels of dapagliflozin typically occurred 1 h post dose
- Dapagliflozin did not affect the pharmacokinetics of verinurad or febuxostat (Figure 4).

Figure 4. Geometric mean (SD) verinurad or febuxostat plasma concentrations over time with or without dapagliflozin

Safety
- 10 subjects had ≥1 adverse events with 16 events in total (verinurad + febuxostat + dapagliflozin, n=7; verinurad + febuxostat + placebo, n=5).
- The most common adverse events were gastrointestinal-related: diarrhea, flatulence, and nausea.
- All adverse events were mild in intensity; no serious adverse events were reported.
- 12 events were treatment emergent adverse events (verinurad + febuxostat + dapagliflozin, n=7; verinurad + febuxostat + placebo, n=5).
- No deaths were reported.
- No clinically relevant changes were seen in laboratory safety measures or vital signs, and no significant elevations in creatinine.

Conclusions
- Addition of dapagliflozin to verinurad + febuxostat in healthy subjects with hyperuricemia significantly reduces serum uric acid concentration.
- Peak uric acid excretion is not significantly affected by dapagliflozin when added to verinurad + febuxostat at the tested doses.
- These findings suggest that dapagliflozin can be safely combined with verinurad + febuxostat without adversely affecting kidney function.