Comparison of APF530, a Subcutaneous Extended-Release Formulation of Granisetron, Versus Intravenous Palonosetron

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BACKGROUND

• Prevention and control of acute and delayed chemotherapy-induced nausea and vomiting (CINV) are cornerstones of supportive care for patients with cancer.
• Although several treatment options exist, there is a need for improved control of CINV.

APF530 is an extended-release tri(ethylene glycol) poly(ortho ester) (TEG-POE)-based polymer formulation containing the 5-HT3 receptor antagonist granisetron and is designed to deliver granisetron over a 5-day period after a single subcutaneous (SC) injection in the abdomen.
• A large phase 3 trial was conducted to compare SC APF530 with intravenous (IV) palonosetron. Primary endpoints included noninferiority to palonosetron in preventing acute and delayed CINV after administration of moderately emetogenic chemotherapy (MEC), and noninferiority in preventing acute CINV after highly emetogenic chemotherapy (HEC). Positive results from this noninferiority study were previously presented.1
• Because assessment of emesis is an important component of best practice in clinical guidelines,2-4 nausea severity and patient satisfaction with nausea control were specifically assessed as key secondary endpoints in this trial.
• A history of prior chemotherapy is one of several patient-related factors associated with increased risk for CINV.2,3 Therefore, a subgroup analysis was performed on this vulnerable chemotherapy-naïve subset of enrolled patients.

METHODOLOGY

Study design: Randomized, multicenter, observer-blind, double-dummy, parallel-group phase 3 study (Figure 1)
Participants: Chemotherapy-naïve or nonnaive men or women ≥18 years old
Chemotherapy and study drug administration
• Patients received single-day treatment with MEC or HEC as defined by Hesketh2 and were stratified at randomization by emetogenicity of chemotherapy.
• For the purpose of the analysis performed here, patients receiving MEC and HEC were combined into a single population.
• APF530 (single SC injection in the abdomen) and palonosetron (IV infusion) or placebo were administered 30 to 60 minutes before chemotherapy.
• Placebo for both SC and IV injections was isotonic saline.
• Standard doses of dexamethasone were administered with each study drug.
• If MEC: Dexamethasone 8 mg IV on Day 1, then once on Days 2-5.
• If HEC: Dexamethasone 20 mg IV on Day 1, then 8 mg PO BID on Days 2-4.

OUTCOME MEASURES

• Complete response (CR) was defined as no emetic episodes and no use of rescue medication. Post-hoc subgroup analysis of data was performed for chemotherapy-naïve and nonnaive patients.
• Patients used a daily diary to record severity of nausea, vomiting/retching episodes, use of rescue medication, and satisfaction with nausea/vomiting control.
• Assessments were made on each treatment day and for the overall 5-day treatment period. Nausea severity was graded as:
° None
° Mildly tolerated, did not interfere with normal daily activities
° Moderate (caused some interference with daily activities)
° Severe (all normal activities completely stopped due to nausea)
• Satisfaction with overall control was scored as:
° Very satisfied
° Satisfied
° Neither satisfied nor dissatisfied
° Dissatisfied
° Very dissatisfied

NAUSEA CONTROL

• APF530 offers comparable nausea control and patient satisfaction to palonosetron over a 5-day period.
• Severity of nausea and patient satisfaction were similar with APF530 and palonosetron after administration of MEC or HEC, regardless of previous chemotherapy exposure.

PATIENT SATISFACTION

• There was no statistical difference between APF530 and palonosetron in nausea severity in either chemotherapy-naïve or chemotherapy-naïve individuals in the combined MEC and HEC population.
• For each day, there were no statistical differences in nausea severity in either arm, in patient subgroups, or in the entire population at an experimental error rate of 0.05 (Figure 3).
• For the entire 5-day period, 65% to 71% of all patients reported a maximum nausea severity of “None” or “Mild” with either treatment (no statistical difference).
• On Day 5, moderate-to-severe nausea was reduced to 13% in APF530 patients and 10% in palonosetron patients regardless of previous exposure to chemotherapy (no statistical difference).

Table 1. Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>MEC (APF530)</th>
<th>Palonosetron</th>
<th>HEC (APF530)</th>
<th>Palonosetron</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT Population (%)</td>
<td>212</td>
<td>208</td>
<td>240</td>
<td>258</td>
</tr>
<tr>
<td>Mean Age ± SD (years)</td>
<td>55 ± 57</td>
<td>57 ± 58</td>
<td>57 ± 58</td>
<td>57 ± 58</td>
</tr>
<tr>
<td>Female (%)</td>
<td>84 ± 83</td>
<td>63 ± 67</td>
<td>61 ± 27</td>
<td>64 ± 24</td>
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<tr>
<td>Ethnicity (%)</td>
<td></td>
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<tr>
<td>Caucasian (%)</td>
<td>59 ± 67</td>
<td>62 ± 61</td>
<td>27 ± 24</td>
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<tr>
<td>Asian (%)</td>
<td>41 ± 33</td>
<td>38 ± 39</td>
<td>73 ± 76</td>
<td>73 ± 76</td>
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<tr>
<td>Prior Chemotherapy (%)</td>
<td>47 ± 49</td>
<td>47 ± 49</td>
<td>58 ± 58</td>
<td>58 ± 58</td>
</tr>
</tbody>
</table>

*Modified intent-to-treat

Table 2. Chemotherapy Regimens

<table>
<thead>
<tr>
<th>MEC% (% of Patients)</th>
<th>MEC% (% of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel + Carboplatin</td>
<td>54</td>
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<tr>
<td>Carboplatin mono- or combination</td>
<td>15</td>
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<tr>
<td>Carboplatin mono- or combination</td>
<td>11</td>
</tr>
<tr>
<td>Docetaxel + Carboplatin</td>
<td>6</td>
</tr>
<tr>
<td>Docetaxel mono- or combination</td>
<td>6</td>
</tr>
<tr>
<td>Carboplatin mono- or combination</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
</tr>
</tbody>
</table>

*Classified per Hesketh criteria.

CONCLUSIONS

• APF530 provides comparable CR rates to palonosetron over the 125-hour period whether or not the patient had previous exposure to chemotherapy.
• Severity of nausea and patient satisfaction were similar with APF530 and palonosetron after administration of MEC or HEC, regardless of previous chemotherapy exposure.
• APF530 offers comparable nausea control and patient satisfaction to palonosetron over a 5-day period.