APF530: Pharmacokinetics and Efficacy of Extended-Release Granisetron Injection in the Prevention of Acute and Delayed Chemotherapy-Induced Nausea and Vomiting

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BACKGROUND

- Unresearched chemotherapy-induced nausea and vomiting (CINV) associated with moderately or highly emetogenic chemotherapy (MEC or HEC) may adversely affect quality of life and chemotherapy adherence.
- In particular, prevention of delayed CINV (dCINV) after chemotherapy remains a clinical challenge.
- Current systemic guidelines recommend a 5-HT3 receptor antagonist (RA) + corticosteroid for patients receiving MEC + a 3-drug combination (5-HT3 RA + neurokinin (NK)/RA + corticosteroid) for patients receiving HEC.

Phase 2 Pharmacokinetic Studies

- Summary methods from phase 2 APF530 trials are shown in Table 1.

Table 1. APF530 Phase 2 Trials

| Trial Design | Population | Treatment | Objective(s) | Safety
|--------------|------------|-----------|--------------|------|
| Phase 2 trial | US sequential | APF530 2% granisetron | Patients (N = 163) + grade ≥ 3 | Treatment
| Phase 2 trial | US sequential | APF530 2% granisetron | Patients (N = 154) | Treatment

Table 2. APF530 Phase 3 Trials

| Trial Design | Population | Treatment | Objective(s) | Safety
|--------------|------------|-----------|--------------|------|
| Phase 3 trial | Multicenter | APF530 2% granisetron | Patients (N = 70) | Treatment
| Phase 3 trial | Multicenter | APF530 2% granisetron | Patients (N = 21) | Treatment

Table 3. MAGIC Trial: Treatment-Emergent Adverse Events

<table>
<thead>
<tr>
<th>APF530 arms</th>
<th>MEC patients</th>
<th>HEC patients</th>
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<tbody>
<tr>
<td>APF530 500 mg SC</td>
<td>10 patients</td>
<td>12 patients</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>2 patients</td>
<td>2 patients</td>
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</tbody>
</table>

Figure 1. APF530: Novel, Extended-Release Polymer Formulation of Granisetron Using Bioerodible[Registered Trademark]

Figure 2. APF530 Phase 2 Trial Design

EFFICACY OF APF530

- In phase 2 trials (N = 85), APF530 dose- proportion granisetron pharmacokinetics and maintained therapeutic granisetron concentrations for at least 144 hours.
- Time to maximum plasma concentration (Tmax) was ~44 hours (range: 33-51) and Tmax (h) was 24-36 hours.
- Median Cmax, exposure, and AUC were similar for APF530 200 and 500 mg in both trials, with no difference between MEC and HEC.

Figure 3. APF530 Pharmacokinetic Profile

PHARMOCINETICS OF APF530

- In the phase 2 trials, the primary efficacy and point was complete response (CR) rate, an assessment of the no nausea or no rescue medication used in the modified intent-to-treat population (ITT). All patients who received study drug and had positive efficacy (CR) were included.
- CR was assessed in acute, delayed, and overall (0-120) phases.

Figure 4. MAGIC Trial: Complete Response Rates In Delayed and Overall Phases of CINV in Patients Receiving HEC

SAFETY

- Safety assessments for all trials included adverse events (AEs) and injection-site reactions (ISRs) (safety population: all patients who received study drug).
- Most common ISRs were bruising and pain; most appeared within 1 to 3 days of injection and resolved by study end.
- In the pharmacokinetic studies, treatment-emergent AEs (TEAEs) were not dose related and were readily mild to moderate.

Noninferiority Trial (ASCO Reactypey)

- In this trial (N = 143), APF530 500 mg was noninferior to palonosetron (Palo) in preventing nausea and delayed CINV after MEC and acute CINV after HEC.
- APF530 was not superior to Palo in preventing delayed CINV after HEC, but CR rates were numerically higher with APF530 500 mg (58.4%) versus Palo (55.3%).

MAGIC Comparative Trial

- Baseline demographics were similar across treatment arms.
- Overall, mean age was 54% (45% to 60%) of patients were female, and 75% had Eastern Cooperative Oncology Group performance status of 0.

Figure 5. Phase 3 MAGIC Trial Design

CONCLUSIONS

- A single SC APF530 injection provides sustained therapeutic granisetron concentrations for 5 days.
- APF530, as part of a probabilistic-recommended 3-drug regimen, demonstrated superiority over Ond in delaying CINV after HEC and was well tolerated.
- Together with the earlier noninferiority trial, results suggest that a single SC injection of APF530 may be a convenient outpatient treatment option for preventing CINV after MEC or HEC.

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REFERENCES