The Prodrug of a Novel Capsid Assembly Modulator (CAM), ALG-000184, Demonstrates a Favorable Nonclinical Toxicokinetic and Toxicology Profile for the Treatment of Chronic Hepatitis B (CHB)

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Background
Capsid assembly modulators (CAMs) represent a clinically validated strategy for inhibiting hepatitis B virus (HBV) RNA encapsidation, leading to reductions in circulating HBV DNA and RNA in infected patients.

ALG-000184 is a prodrug of ALG-001075, a novel potent CAM-E (empty), which demonstrated excellent physicochemical properties with high aqueous solubility, good oral bioavailability, and efficient conversion to ALG-001075 in all species studied to date. A favorable toxicology profile and potent suppression of HBV DNA in CHB subjects has supported advancement of ALG-00184 into longer-duration clinical trials in CHB patients.

Methods
Repeat dose toxicology studies with ALG-000184 were conducted in rats (4-, 13-, 26-weeks) and dogs (4-, 13-, 39-weeks) following daily PO doses. Reproductive toxicology studies were conducted in Sprague-Dawley rats (0-24 hr) and in rabbit, monkey and human. Repeat dose toxicology studies with ALG-000184 were conducted in rats prior to mating and continuing through 1 day prior to euthanasia while females were dosed for 14 days prior to mating and continuing through gestation day (GD) 6-17 in rats and GD7-20 in rabbits; in the rat fertility study, males were dosed for 28 days prior to mating and continuing through 1 day prior to euthanasia while females were dosed for 14 days prior to mating and continuing through gestation day. For these studies, ALG-00184 was formulated in phosphate buffered saline (PBS).

ALG-000184 demonstrated a favorable toxicology profile

<table>
<thead>
<tr>
<th>Species</th>
<th>Duration</th>
<th>ALG-001075 Doses (mg/kg/day)*</th>
<th>NOAEL Steady-State ALG-001075 AUC0-24 (ng·hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>4-week</td>
<td>0 (vehicle), 5, 15, 100</td>
<td>97,600 (M), 523,000 (F)</td>
</tr>
<tr>
<td>Dog</td>
<td>4-week</td>
<td>0 (vehicle), 5, 15, 30</td>
<td>199,000</td>
</tr>
<tr>
<td>Rat</td>
<td>13-week</td>
<td>0 (vehicle), 10, 25, 100, 100/75</td>
<td>315,000</td>
</tr>
<tr>
<td>Dog</td>
<td>13-week</td>
<td>0 (vehicle), 10, 20, 40</td>
<td>242,000</td>
</tr>
<tr>
<td>Rat</td>
<td>26-week</td>
<td>0 (vehicle), 5, 10, 30</td>
<td>160,000</td>
</tr>
</tbody>
</table>

Note: The NOAEL or NOAEL dose, when identified in the study, is designated by underlined text.

ALG-000184 generally well tolerated in repeat dose studies

- Well-tolerated in rats up to the highest dose tested (150 mg/kg/day)
- Well-tolerated in dogs, except at the highest dose (≥ 40 mg/kg/day; ALG-001075 AUC0-24 ≥ 484,000 ng·hr/mL)
- No genotoxicity: Negative in Ames, in vitro micronucleus test (MNT) and in vivo rat MNT
- Safety Pharmacology: No cardiovascular, respiratory or CNS effects noted up to the highest doses (150 mg/kg/day in rats and 50 mg/kg/day in dogs)
- No in vitro photocytotoxic potential
- Adequate coverage for major metabolite ALG-000302 in nonclinical species

Dose proportional increases in ALG-001075 plasma exposures with little to no accumulation in repeat dose toxicity study

- ALG-000184 generally well tolerated in repeat dose studies

- No effects in embryo fetal development in rodent or rabbits up to the highest doses tested
- No effects in fertility studies in rats up to the highest doses tested

Conclusions
- ALG-001075 plasma exposure was high and increased with ALG-000184 dose over the dose range studied, providing a significant exposure margin from clinical doses.
- Target organ toxicities occurred at plasma exposures (AUC0-24 of ALG-001075 that were ≥ 9-fold above clinically efficacious exposures (AUC0-24)) where significant inhibition of HBV DNA is noted in CHB patients.
- ALG-000184 did not have effects in either rat or rabbit embryofetal development studies or rat fertility studies.
- Overall, a favorable toxicology profile has supported ALG-000184 to advance into longer-duration clinical trials in CHB patients.

References

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ALG-001075 in all species studied to date. A favorable toxicology profile and potent suppression of HBV DNA in CHB subjects has supported advancement of ALG-00184 into longer-duration clinical trials in CHB patients.

High ALG-001075 exposure was achieved with ALG-000184 oral dosing in PBS solution.

ALG-001075 is well distributed with good free fraction and liver partitioning.

Metabolism mainly via CYP3A4 mediated oxidative pathways, with one major oxidative metabolite, ALG-000302, and confirmed in vivo in mouse, rabbit, monkey and human.

Multiple routes of excretion in rat, while biliary excretion was the major route of elimination in dogs.

Low CYP and transporter-mediated drug-drug interactions potential.

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