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-000184 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 and NZW rabbits with daily PO dosing. Dosing for embryofetal development studies occurred from 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 GD7. For these studies, ALG-000184 was formulated in phosphate buffered saline (PBS).

ALG-000184 demonstrated good oral bioavailability of ALG-001075 in all nonclinical species

Parameter	Mouse	Rat	Rabbit	Dog	Monkey
ALG-000184 Dose (mg/kg)	37.8	37.8	6.3	6.3	6.3
ALG-001075 T_{max} (hr)	0.50	1.00	1.67	1.17	1.33
ALG-001075 C_{max} (ng/mL)	8,214	5,673	703	2,717	1,387
ALG-001075 AUC_{last} (ng.h/mL)	28,984	34,649	4,291	33,385	3,904
ALG-001075 $t_{1/2}$ (hr)	2.08	2.19	5.38	10.4	2.03
%F	70.7	41.6	NA	81.7	35.0

- **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**

ALG-000184 demonstrated a favorable toxicology profile

Species	Duration	ALG-000184 Doses (mg/kg/day)[a]	NOAEL Steady-State ALG-001075 AUC_{0-24} (ng·hr/mL)
Rat	4-week	0 (vehicle), 10, 25, 50, 150	315,000
	13-week	0 (vehicle), 10, 25[b], 50[b], 100/75	97,600 (M)/ 523,000 (F)
	26-week	0 (vehicle), 5, 15, 30	199,000
Dog	4-week	0 (vehicle), 3, 10, 25, 50	274,000
	13-week	0 (vehicle), 3, 10, 20, 40	262,000
	39-week	0 (vehicle), 3, 7.5, 15	160,000

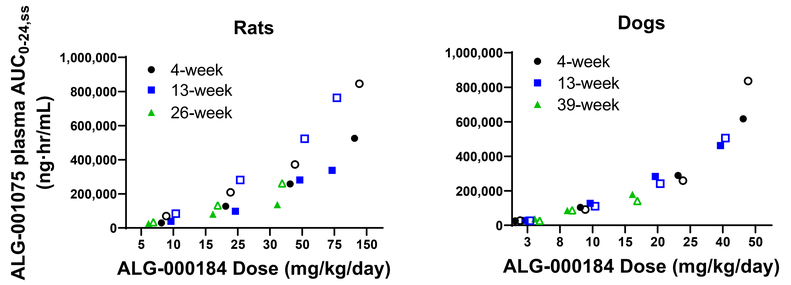
NOAEL: No Observed Adverse Effect Level
[a] The NOEL or NOAEL dose, when identified in the study, is designated by underlined text.
[b] NOEL differed by sex: 25 mg/kg/day in males; 50 mg/kg/day in females.

- **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 tested (150 mg/kg/day in rats and 50 mg/kg/day in dogs)**
- **No in vitro phototoxicity potential**
- **Adequate coverage for major metabolite ALG-000302 in nonclinical species**

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 AUC_{0-24} ≥ 484,000 ng·h/mL)**
  - **In 13-week study, the 40 mg/kg/day group was terminated early on Day 78 because 10 of 12 dogs had systemic inflammation, similar to that noted in 1 dog in the 4-week study at 50 mg/kg/day**
  - **Effects were reversible within 2 weeks upon dosing holiday or treatment with anti inflammatory agent**
- **Histopathology findings were partially reversible and considered monitorable**
  - **Kidney findings in rats at ≥ 50 mg/kg/day (ALG-001075 AUC_{0-24} ≥ 402,000 ng·h/mL) and in dogs at 40 mg/kg/day**
    - **Rat: tubular degeneration/regeneration, tubular basophilia, and cortical tubular dilatation, possibly representing an exacerbation of rodent chronic progressive nephropathy**
    - **Dog: calculi and pyelitis in renal papilla and pelvis, consistent with route of elimination at high systemic exposures**
  - **Systemic inflammation in dogs at 40 mg/kg/day consistent with reactive histiocytosis**
- **No target organ toxicities were noted in chronic toxicity study in rats up to 30 mg/kg/day (ALG-001075 AUC_{0-24} 199,000 ng·h/mL) or dogs up to 15 mg/kg/day (ALG-001075 AUC_{0-24} 160,000 ng·h/mL), the highest doses tested**

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



Males represented in solid symbols and females in open symbols for both species

ALG-000184 did not affect any reproductive parameters

Species	Duration	ALG-000184 Doses tested (mg/kg/day)[a]	NOAEL Steady-State ALG-001075 AUC_{0-24} (ng·hr/mL)
Rat	EFD	0 (vehicle), 3, 10, 25[b]	169,000
Rabbit	EFD	0 (vehicle), 20, 50, 100[c]	89,700
Rat	Fertility	0 (vehicle), 10, 25, 75[d]	398,000

EFD-embryo fetal developmental studies
[a] The NOEL or NOAEL dose, when identified in the study, is designated by underlined text
[b] mg/kg/gestation day (GD) 6-17;[c] mg/kg/GD7-20, [d] mg/kg/GD7

- **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 (AUC_{0-24}) of ALG-001075 that were ≥ 9-fold above clinically efficacious exposures (AUC_{0-24}) 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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