A new oral prodrug of the Aβ aggregation modulator GAL-201 shows significantly improved pharmacokinetic profile

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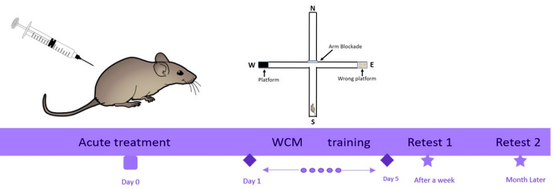
BACKGROUND

GAL-201, a small molecule in development as an oral therapy for Alzheimer's disease (AD), and currently in preclinical testing, inhibits the formation of soluble, toxic Aβ species and thereby prevents neurodegeneration. Studies in different AD models indicate a pharmacological effect mediated by peak plasma concentrations (C_{max})[1,2]. In tgArcSwe AD mice, the cognitive performance improved significantly, comparable to the level in wild-type mice, after a single subcutaneous administration of GAL-201[2].

Figure 1: Single GAL-201 injection significantly improves cognitive performance in transgenic AD mice

A)



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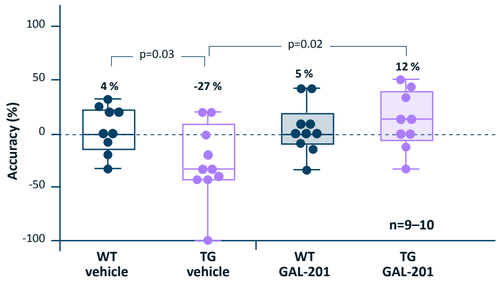


WT = wild type mice
TG = tgArcSwe mice bearing the APPswe and ArcAb mutation, 12 months old
GAL-201 was injected at 80 mg/kg one day before the behavioral experiment

A) Cognitive performance was measured in the water-cross maze by the percentage of correct decisions for left and right, called "Accuracy".
B) tgArcSwe mice showed a significantly reduced accuracy compared to age-matched wild-type mice. Injection of GAL-201 improved the cognitive performancein tgArcSwe mice significantly comparable to the level in wild-type mice.

OBJECTIVES

The oral bioavailability of GAL-201 in rats is acceptable [1], however, a better bioavailability would reduce oral drug load, which would ultimately be an advantage for patients.

METHODS

New derivatives of GAL-201 were created based on rational design to generate prodrug candidates. These were pharmacokinetically evaluated in Wistar rats after applying 10 mg/kg GAL-201 equivalent. Plasma concentrations of prodrugs and parent compound (GAL-201) were measured, and time-course profiles of the two lead candidates are reported.

Figure 2: Two leading prodrug candidates: Carbamate-Ester-Analogue (= Prodrug 1) and Ethyl-Carbamate-Analogue (= Prodrug 2)

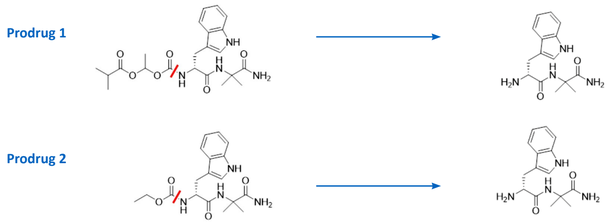
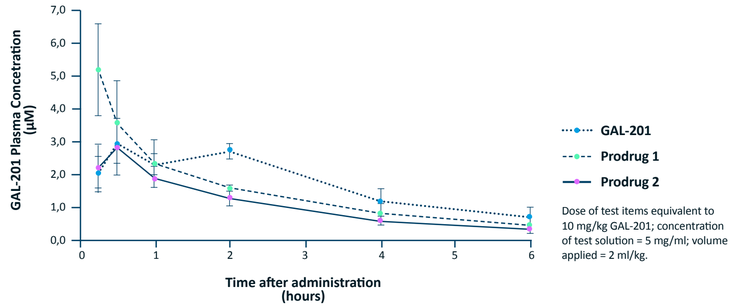


Figure 3: Plasma concentration of GAL-201 after oral administration of test items

Both prodrugs were rapidly absorbed, avoiding the biphasic absorption typical for GAL-201, as seen after 2 hours. But Prodrug 1 already after 15 minutes reached a ~70 % higher C_{max} than Prodrug 2 as well as GAL-201 reached after 30 minutes.



Dose of test items equivalent to 10 mg/kg GAL-201; concentration of test solution = 5 mg/ml; volume applied = 2 ml/kg.

Figure 4: Total systemic exposure (AUC) of GAL-201 and its prodrugs

Bars show mean AUC (nmol/mL*h) ± variability; stacked bars indicate the relative contributions of parent GAL-201 (blue) and prodrug (pink). With GAL-201, total systemic exposure was higher than with its prodrugs, likely due to the slow, biphasic absorption. While GAL-201 was completely released (100 % degradation) from Prodrug 1 ~ 20 % of Prodrug 2 remained undegraded, meaning that only ~ 80 % of GAL-201 was released from Prodrug 2.

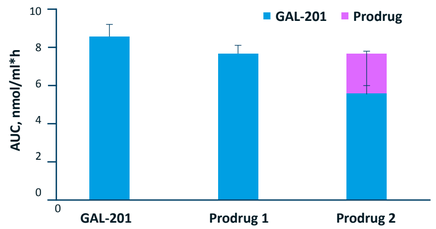
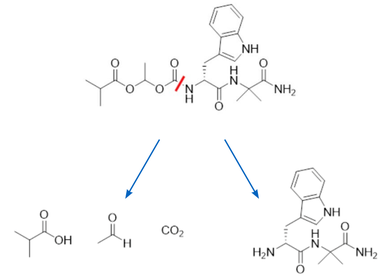


Figure 5: Rationale for the Carbamate-Ester-Analogue

The carbamate moiety (shown left from the orange line) is known from gabapentin enacarbil, which was approved in 2012. While chemically stable as solid, in the body the enacarbil prodrug is rapidly degraded into gabapentin, leading to a transport via high-capacity transporters[3]. The carbamate moiety is cleaved rapidly by hydrolysis into isobutyric acid, CO_2, and acetaldehyde – metabolites which are "Generally Recognized as Safe" by the FDA[4].



RESULTS

Prodrug 1 was fully absorbed from the stomach of Wistar rats within 15 minutes after intake, achieving a ~70% higher C_{max} than the parent compound at 30 minutes, with 100% degradation into GAL-201. In contrast, Prodrug 2 peaked at 30 minutes, but degradation reached only ~80%. Both prodrugs were rapidly absorbed from the stomach and avoided the biphasic absorption seen with the parent compound, providing an improved pharmacokinetic profile, considering the peak-level driven MoA of GAL-201.

CONCLUSIONS

Prodrug 1 demonstrated rapid and complete absorption, yielding a faster peak (15 minutes) and ~70% higher Cmax compared to the parent compound. In contrast, Prodrug 2 showed incomplete absorption and did not reach a higher peak than GAL-201. Unlike the slow, biphasic absorption of GAL-201, Prodrug 1 was immediately absorbed and fully converted, leading to a substantially higher systemic drug level and supporting the peak level driven MoA of GAL-201. This superior PK profile enables a significantly reduced oral dosing amount. Prodrug 1 therefore represents a promising new oral Aβ-targeting AD drug development candidate.

References:
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