Development of AL01211, an oral, non-brain penetrant glucosylceramide synthase inhibitor (GCSi), to treat Fabry disease

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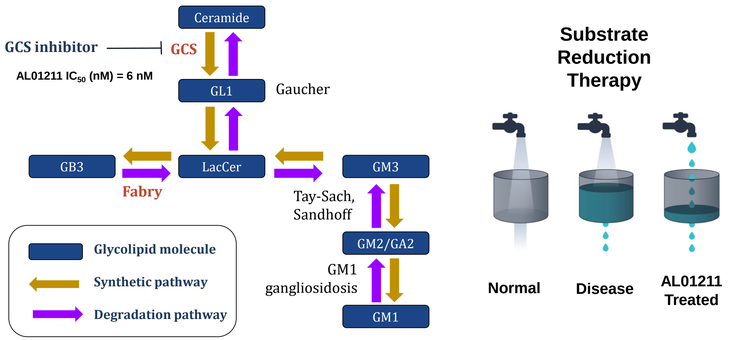
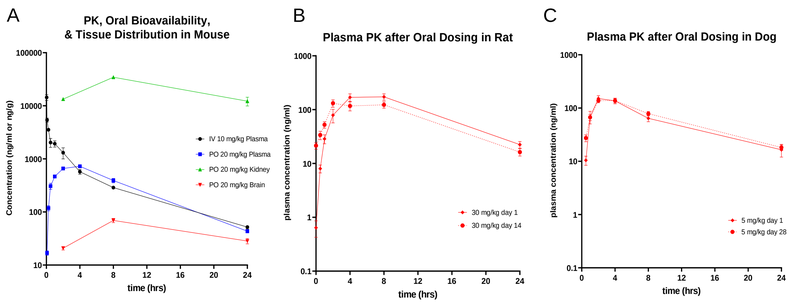
Fabry disease, a rare lysosomal storage disorder caused by reduced activity of the enzyme α-galactosidase A (GalA), is characterized by accumulation of globotriaosylceramide (GL3) and lyso-globotriaosylceramide (lyso-GL3) resulting in a wide range of symptoms from pain, gastrointestinal issues, kidney failure, heart disease, and stroke. Enzyme replacement therapy (ERT), the current standard of care, reduces GL3 and lyso-GL3, and improves many symptoms but patients can continue to develop progressive renal and cardiac disease. Glucosylceramide synthase inhibitors (GCSi) reduce glycosphingolipid (GSL) production, including GL3 and lyso-GL3, and have the potential to become a new treatment paradigm for Fabry disease. AL01211 is a novel oral, non-brain penetrant GCSi being developed for the treatment of Fabry disease. AL01211 inhibits GCS activity with an IC50 of approximately 7 nM in GCS activity assays without significant off-target activity to other targets and pathways of safety concern. The pharmacokinetics of AL01211 supports once daily, oral administration in human. Oral dosing of AL01211 efficiently reduces GSL production in mouse, rat, and dog kidney with minimal effects on brain GSL levels. In a Fabry disease mouse model, AL01211 reduces GL3 and lyso-GL3 levels in kidney, heart, and other peripheral organs while having minimal effects in the brain. Phase I clinical trials in healthy human subjects, consisting of oral administration of AL01211 (single ascending dose and 14-day multiple ascending dose study), demonstrated that AL01211 was overall safe, well-tolerated, exhibiting dose-dependent PK and PD properties. In conclusion, AL01211 is a novel, orally available, potent and selective, non-brain penetrant GCSi. The increased potency and low brain penetration make AL01211 a potentially safer and more efficacious molecule for treating Fabry disease patients, especially in younger patients seeking a convenient and life-long treatment option.

GCS inhibition as substrate reduction therapy for glycosphingolipid storage disorders

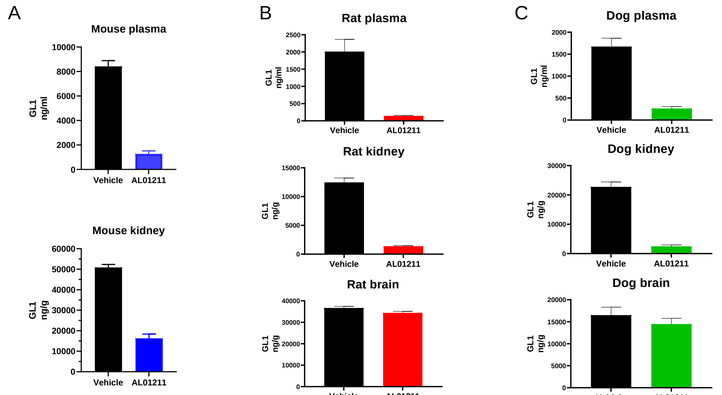


Pharmacokinetic properties of AL01211 support once daily oral dosing



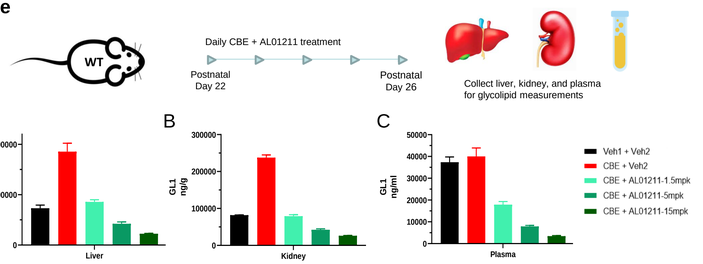
Pharmacokinetic profiles of AL01211 in mouse, rat, and dog. Oral bioavailability of AL01211 is 34% in mice and AL01211 readily distributes into peripheral tissues like kidney while brain levels remain low **(A)**. Pharmacokinetic profile of AL01211 in rat **(B)** and dog **(C)** after single or multiple oral doses.

AL01211 efficiently reduces glucosylceramide (GL1) in plasma and kidney without significantly impacting brain GL1



Pharmacodynamic effects of AL01211 in wild type mouse, rat, and dog. Mice were treated for 7 days and GL1 was measured in plasma and kidney by LCMS **(A).** Rat and dog were treated with AL01211 daily for 14 days and GL1 was measured in plasma, kidney, and brain using LC-MS/MS **(B and C).**

AL01211 reduces glucosylceramide (GL1) in a pharmacological model of Gaucher disease



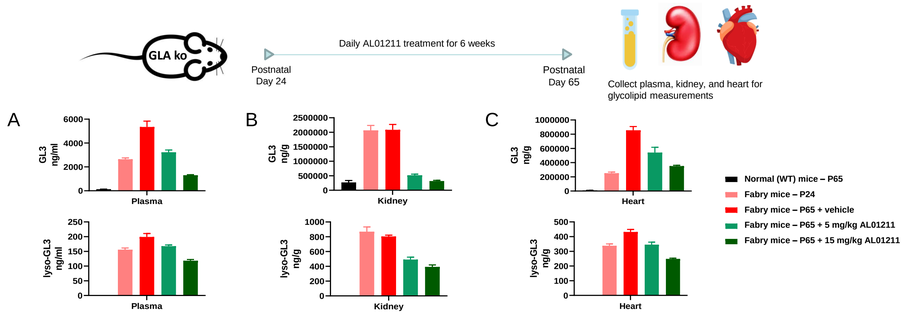
Pharmacokinetic effects of AL01211 in a pharmacological Gaucher disease model. Mice aged to postnatal day 22 were administered Conduritol Beta Epoxide (CBE), a covalent inhibitor of the lysosomal enzyme GBA1, for 5 days. CBE injection resulted in accumulation of GL1 in tissues. Coadministration of CBE and AL01211 dose dependently reduced GL1 levels in liver **(A)**, kidney **(B)**, and plasma **(C)**.

AL01211 is highly specific for GCS

Selectivity (off-target activities) of AL01211

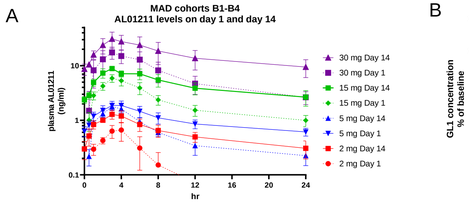
- Generally clean in 78-molecular target Eurofins SAFETYscan screen panel
- Also assessed off-target activity against enzymes that are involved in relevant pathways
  - No activity against GBA1 and GBA2
  - Activity against intestinal disaccharidases are currently ongoing, although AL01211 is not an iminosugar analog and should not impact these enzymes
- IC_{50} or EC_{50} are greater than 3 μM for all targets

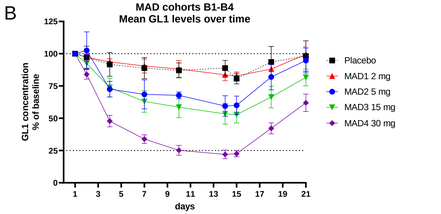
AL01211 reduces globotriaosylceramide (GL3) and lyso-GL3 in a Fabry Disease mouse model



Pharmacodynamic effects of AL01211 in Fabry mouse model. GLA knockout mice were treated with AL01211 for 6 weeks, from postnatal day 24 to postnatal day 65, and total GL3 was measured in plasma **(A)**, kidney **(B)**, and heart **(C)** by LC-MS/MS.

Pharmacokinetic, pharmacodynamic, and safety results from the AL01211 Phase 1 Healthy Volunteer Study (NCT04908462)





C Safety summary (MAD)

- Overall, there were 23 AEs in 13 (40.6%) of 32 participants, which were mostly Grade 1 and Grade 2 TEAEs.
- The most common AE was headache in both groups: 8 (29.0%) in all AL01211 treatment groups and 2 (20%) in the placebo group.
- The second most common TEAEs are gastrointestinal disorders: 5 (18.5%) in all AL01211 treatment group and 3 (30%) in placebo group.
- There were no trends in the incidence of treatment-related TEAEs according to the dose of AL01211 or between the placebo and AL01211 treated groups.
- There were no SAEs, life-threatening events, severe TEAEs, or TEAEs leading to death.

PK, PD, and safety of AL01211 phase 1: Pharmacokinetic profiles of AL01211 in plasma showed increasing exposure with increasing dose level on day 1 and day 14 **(A)**. Increasing exposure inversely correlated with a greater pharmacodynamic effect as measure by plasma GL1 levels **(B)**. The safety profile of AL01211 was clean with no significant or serious adverse events recorded **(C)**.

Conclusions

Conclusion: AL01211 is a novel, orally available, potent, and selective GCSi that efficiently reduces GSL in the kidneys and heart of animal models but does not significantly enter the brain. Increased potency and low brain penetration make AL01211 a potentially safer and more efficacious molecule for treating Fabry disease patients, especially in young Fabry patients seeking a convenient, lifelong treatment option. A Phase I clinical trial, consisting of daily oral administration of AL01211 (single ascending dose and 14-day multiple ascending dose study) in healthy volunteers was recently completed showing clear PK/PD relationship and a clean safety profile.

References

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