An ALK7 siRNA Developed by SiranBio Adipose Delivery Platform Showed Excellent Potency and Safety Profile in Pre-Clinical Studies

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Introduction

Obesity is a major risk factor for many chronic diseases, including MAFLD, diabetes, cardiovascular disease, hypertension, stroke, and certain cancers [1]. In recent years, GLP-1 agonists such as Semaglutide and Tirzepatide have been extremely successful in body weight control. However, they are still encountering problems of muscle loss and body weight regain.

ALK7 (ACVR1C) belongs to TGF-β type I receptor. It is highly expressed in white and brown adipose tissue. Inhibition of ALK7 promotes lipolysis and maintains lean body mass [2]. ALK-7 inhibitors may help to solve the problems of GLP-1 agonists. Therefore we invented Stork-F, a platform technology for the adipose targeting of siRNA, and developed **SA030, a siRNA drug targeting ALK-7 mRNA.**

Here we report data for our Stork-F technology, and the efficacy and safety profiles of SA030 in animal studies.

Methods

Pharmacokinetics (PK) study: SA030 was injected subcutaneously (SC) at 0.3, 1, 3, 9 mpk single dose in C57BL/6J mice. The concentration of SA030 in multiple tissues were detected.

Pharmacodynamic (PD) study in DIO mice: C57BL/6J mice were fed with high-fat diet (HFD) to induce obesity. Mice were divided into two groups, with PBS and ALK-7 siRNA (3 mg/kg, SC, QW). Body weight and food uptake were monitored.

PD study in DIO non-human primates (NHP) : NHP were fed with HFD to induce obesity. These NHP were dosed with PBS or SA030 (9 mpk, SC, single dose). Body weight, liver biopsy and other tests were done.

ALK7 inhibition activity study: SA030 was injected SC in NHP at 3mpk, ACVR1C mRNA of adipose tissue were detected by qPCR method.

Toxicity studies: Safety profile, such as biochemistry, routine blood test and histopathology were assessed in rat and cynomolgus monkeys with SA030 100 mg/kg Q2W for 3 doses.

All studies are ongoing.

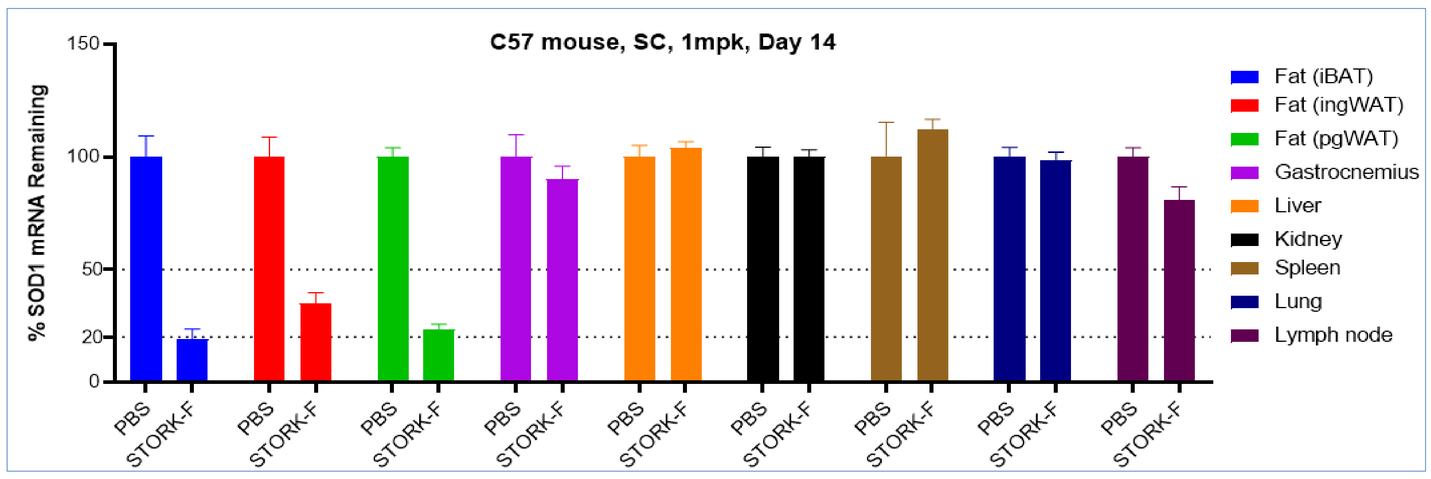
Results

SA030 Has High Exposure in Adipose Tissue

- ✓ Tissue distribution: SA030 showed predominant distribution in adipose tissues (ingWAT and pgWAT). The concentrations of SA030 exhibited a clear dose-dependent increase across all tested doses (0.3–9 mpk), with higher doses yielding significantly greater exposure. SA030 could be detected in other tissues (lung, muscle, heart), much lower compared to adipose tissues and metabolic organs.
- ✓ These results demonstrates the tissue-specific distribution of siRNA by Stork-F technology, SiranBio's proprietary platform for the adipose delivery.

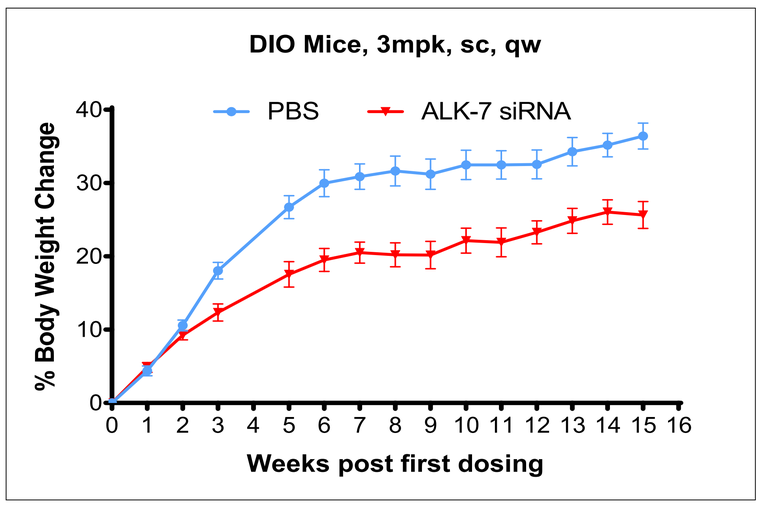
Results

SiranBio Adipose Delivery Platform, Stork-F, Is Potent and Selective for Fat



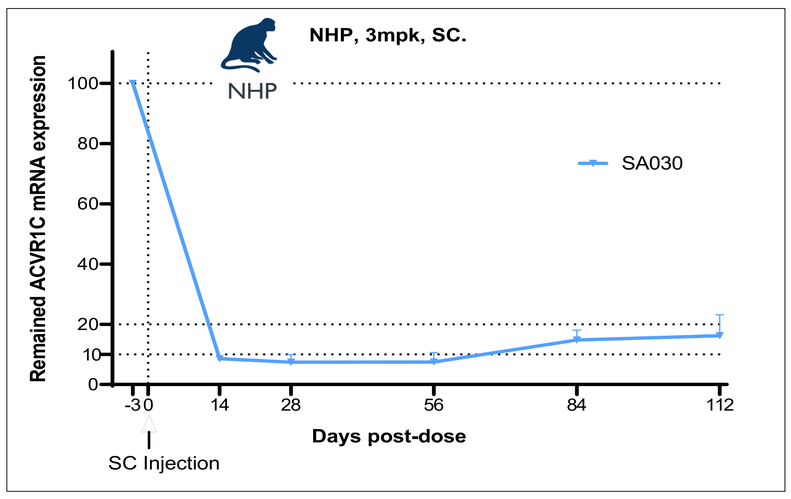
- ✓ Stork-F technology effectively silenced mRNA in all types of adipose, with good tissue selectivity.

Sustained Weight Control in DIO Mice



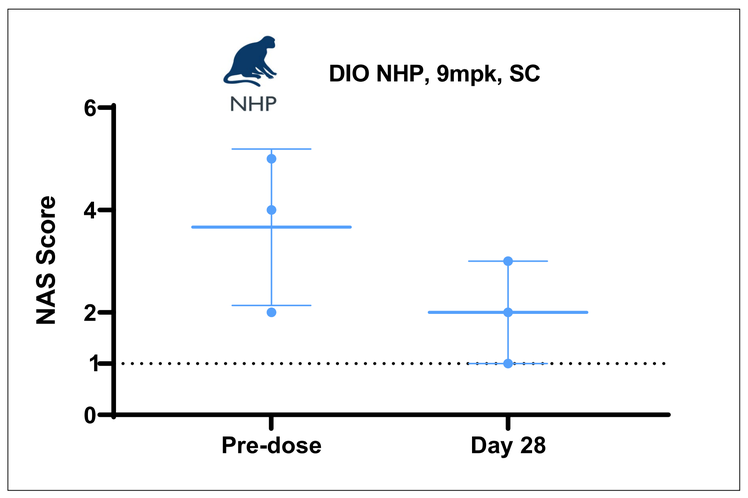
- ✓ ALK-7 siRNA (3mpk, QW) showed sustained weight control in DIO mice.
- ✓ ALK-7 siRNA does not influence cumulative food uptake compared to PBS (data not shown).

Long-Lasting mRNA Silencing in NHP



- ✓ Single injection of SA030 (3mpk) decreased ACVR1C mRNA levels for > 80%, and lasted for more than 4 months.

SA030 Decreased NAS Score in DIO NHP



SA030 Was Well-Tolerated

- ✓ Non-GLP toxicity studies, no mortality, no obvious change in body weight/ food intake or behavior, no SA030 related significant changes in clinical chemistry were observed.
- ✓ Minimal histopathological change of liver Kupffer cell hypertrophy in rats was observed, which is common in siRNA therapeutics.

➢ (Left) SA030 treatment resulted in rapid and significant reduction of NAS score in DIO NHPs, indicating its potential therapeutic benefits for MAFLD.

Conclusions

- ✓ ALK-7 siRNA could effectively suppresses body weight gain over 16 weeks without affecting food intake in DIO mice;
- ✓ In NHPs, single injection of SA030 can inhibit ACVR1C mRNA in adipose tissue for > 4 months, with E_{max} over 90%;
- ✓ SA030 significantly reduces NAS scores in obese NHPs, indicating its potential applications in the treatment of MAFLD;
- ✓ SA030 further validated the adipose delivery platform Stork-F, with high exposure in fat;
- ✓ SA030 exhibited favorable safety profiles, with no significant toxicological risks observed in rat and cynomolgus monkey toxicity studies.
- ✓ These findings support SA030 as a novel therapeutic candidate for obesity treatment, and may help to solve the adverse effects of GLP-1RAs in combination therapies.

Acknowledgements

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References

[1] A 2022 update on the epidemiology of obesity and a call to action: as its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on.

[2] Targeting activin receptor-like kinase 7 ameliorates adiposity and associated metabolic disorders.

Contact Information

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