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Overview of nonclinical studies of LIB-01, a novel promising oral drug under development for treatment of erectile dysfunction

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Introduction

LIB-01 is a novel molecule being developed as an oral drug for the treatment of erectile dysfunction (ED).

LIB-01 is a semi-synthetic analog, developed based on research on active compounds identified in root bark that had been used for treatment of male sexual disability since time immemorial.

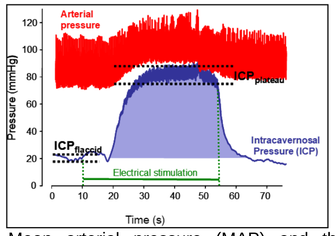
Aim

In preparation for clinical development, nonclinical studies on erectile function were conducted in normal and diabetic rats with ED. Studies to investigate the mechanism supporting the pro-erectile effect of LIB-01 were also conducted.

A summary of the results from the nonclinical research program is presented.

Methods

Erectile response elicited by repeated electrical stimulations at various frequencies of the cavernous nerve (ES CN) in anaesthetized control Wistar and Goto-Kakizaki (GK), a type 2 diabetes model, ED rats was assessed. Intracavernosal and arterial blood pressures were monitored according to a standardized experimental procedure.



Mean arterial pressure (MAP) and the amplitude of the erectile responses elicited by each ES CN were quantified for each rat and averaged for each experimental group.

Mechanism of action studies were conducted with rat cavernosal tissue samples using immunohistochemistry and in *ex vivo*/organ chamber experiments.

The isometric tension studies were conducted on cavernosal strips from LIB-01 treated and untreated Wistar rats. Cavernosal strips from untreated rats were incubated with either LIB-01 or DMSO (control) and then pre-contracted by phenylephrine (PHE).

Concentration- or frequency response curves were performed on PHE pre-contracted strips in 3 consecutive steps:

(i) cumulative addition of increasing acetylcholine (ACh) concentrations

(ii) electrical field stimulation (EFS) with increasing frequencies

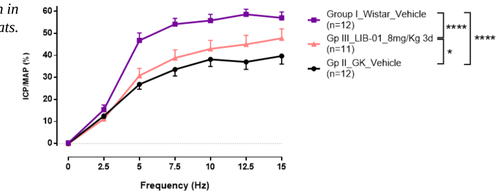
(iii) cumulative addition of increasing sodium nitroprusside (SNP) concentrations

Results

A statistically significant pro-erectile facilitatory effect of LIB-01 has been repeatedly evidenced in all the studies conducted in anaesthetized adult control Wistar rats, by oral or subcutaneous administration of LIB-01 at 15 mg/kg/d, with an effect in the similar range as *iv* sildenafil 0.3mg/kg, when compared.

In addition, LIB-01 significantly improved erectile responses in adult anaesthetized diabetic GK ED rats compared to vehicle-treated rats, demonstrating the pro-erectile effect of LIB-01 in a robust validated pathophysiological rat model of type 2 diabetes (Figure 1).

Fig 1. LIB-01 improves erectile function in diabetic GK ED rats.



The pro-erectile effect of LIB-01 is not acute, instead, LIB-01 displays a delayed onset of effect where the effect increases over time post administration and remains over a period of at least 7 days (Figure 2).

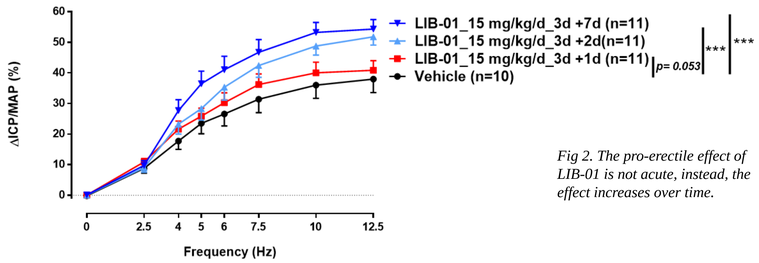


Fig 2. The pro-erectile effect of LIB-01 is not acute, instead, the effect increases over time.

Immunohistochemistry experiments on rat's cavernosal strips from LIB-01 treated normal rats showed that neither CD31 nor nNOS expression was altered (Figure 4), thus likely ruling out any effect of LIB-01 on cavernosal micro-vascularization or cavernosal nNOS.

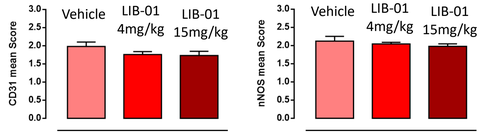
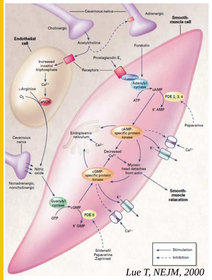


Fig 4. LIB-01 did not alter CD31 or nNOS expression in cavernosal tissue.

Furthermore, only at a high concentration (10^{-5} M) was there a slight increase in the endothelium dependent relaxations induced by ACh compared to vehicle (Figure 5) while LIB-01 did not exert any effect neither on endothelium-independent relaxations induced by SNP nor on nitrergic relaxation induced by EFS of untreated rat's cavernosal strips, exposed *ex vivo* to different concentrations of LIB-01.



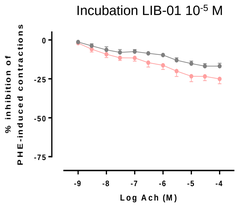


Fig 5. Only at 10^{-5}M, LIB-01 increased the endothelium dependent relaxations induced by ACh.
Note that the relaxant effects were observed at high concentrations of LIB-01.

Conclusion

- LIB-01 is a novel compound which displays a significant pro-erectile effect in anesthetized normal rats as well as in diabetic rats with ED.
- The pro-erectile effect of LIB-01 is not acute, instead, the effect increases over time and remains for at least 7 days.
- Results from several mechanistic studies lead to postulate that the mechanism of LIB-01 does not recruit the NO-cGMP pathway thereby differing from phosphodiesterase type 5 inhibitors.
- A first-in-human clinical trial with LIB-01 was initiated in August 2023.

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