LG Chem
Life Sciences Company

First Oral MC4R Agonist for the Treatment of Rare Genetic Obesity

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Abstract: 1920-P

American Diabetes Association.

80TH SCIENTIFIC SESSIONS
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FINANCIAL DISCLOSURE

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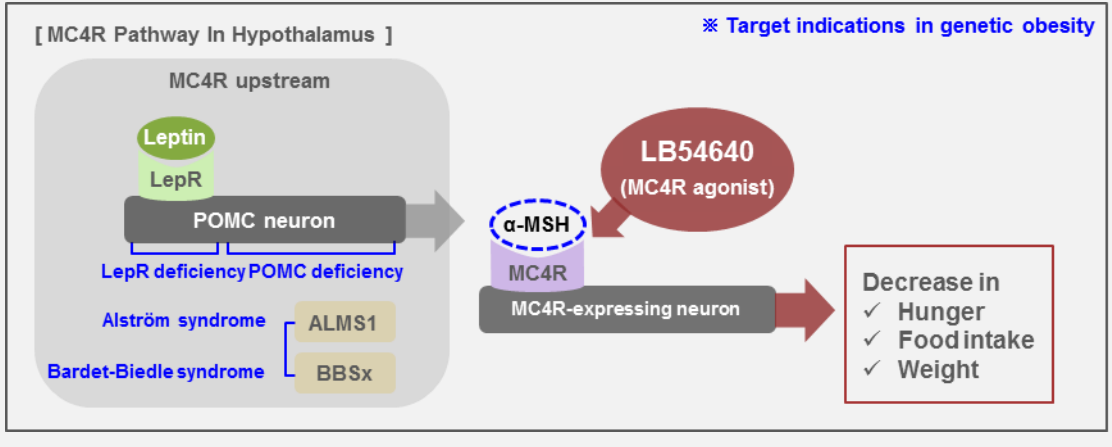
INTRODUCTION

Background

- MC4R pathway defects result in severe hyperphagia and life-threatening obesity.
- MC4R agonist has a potential for regulating weight and hunger in rare genetic disorder of obesity.
- **LB54640 is the first oral MC4R agonist, aiming for best-in-class through the advantage of oral administration and improved safety profile.**



Objective

To assess the efficacy, pharmacokinetic profiles and safety of LB54640, which is an orally available, small molecule MC4R agonist under the clinical development.

Methods

- Efficacy of LB54640 has been evaluated in rodent models of obesity compared to in-class competitor.

- Pharmacokinetic profiles of LB54640 have been examined in mouse, rat, dog and monkeys after single dose.

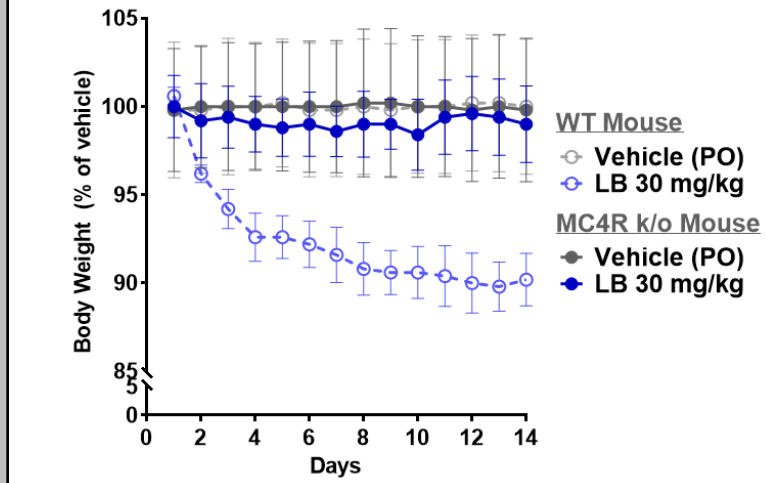
- Safety of LB54640 has been evaluated by GLP toxicity studies including repeated dose toxicity, genotoxicity and safety pharmacology.

RESULTS (ON-TARGET EFFECT CONFIRMATION USING MC4R K/O MICE)

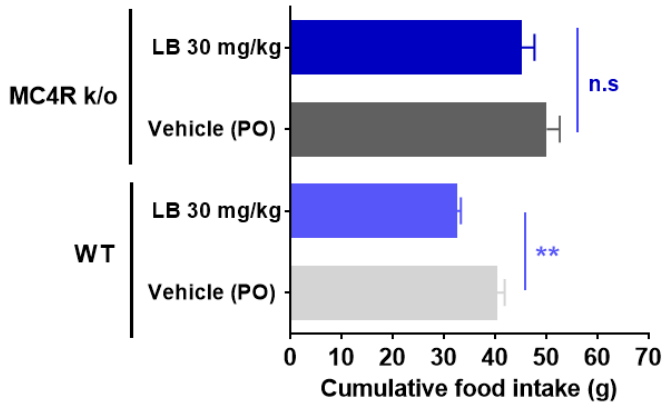
- The weight loss effects have completely disappeared in MC4R k/o mice.
- It demonstrates that LB54640 acts through the on-target effect in the MC4R pathway.

To verify the on-target effect of LB54640 on MC4R using MC4R knock-out mice

Body weight change (2 Weeks)



Food intake (2 Weeks)



WT mice and MC4R k/o mice were fed with high fat diet for 19 weeks and 4 weeks, respectively.

LB: LB54640 (LG Chem), oral small molecule, once a day

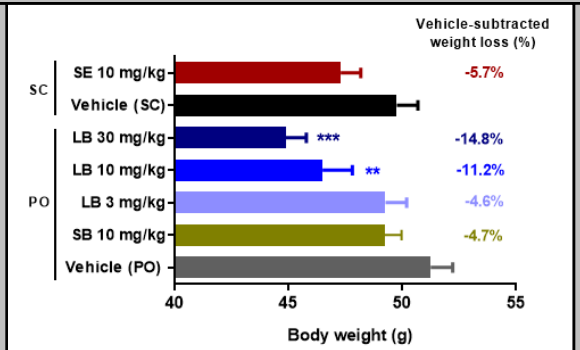
Mean±SEM, Unpaired Student t-test, two-tailed (*p<0.05, **p<0.01, ***p<0.001)

RESULTS (EFFICACY IN DIO MICE)

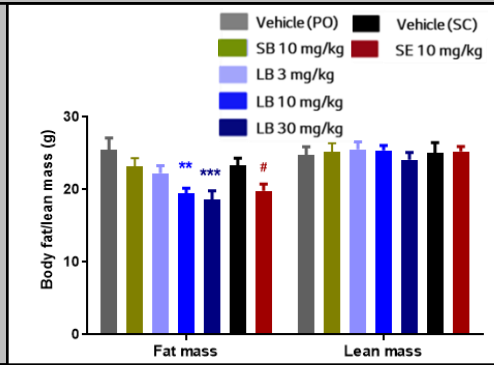
- Once daily administration of LB54640 led to substantial appetite suppression and weight loss in DIO mice.

To evaluate the anti-obesity efficacy of repeated administration of LB54640 in DIO mice

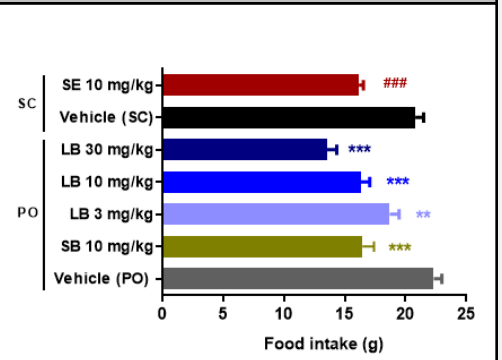
Body weight (Week 6)



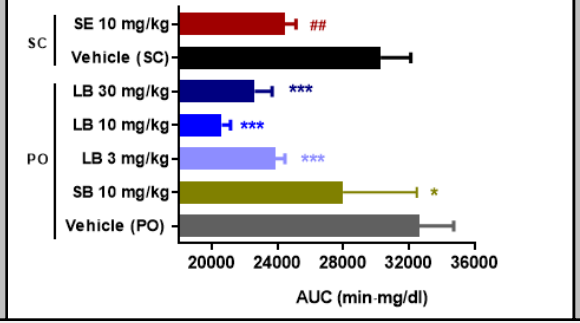
Fat/Lean mass (Week 6)



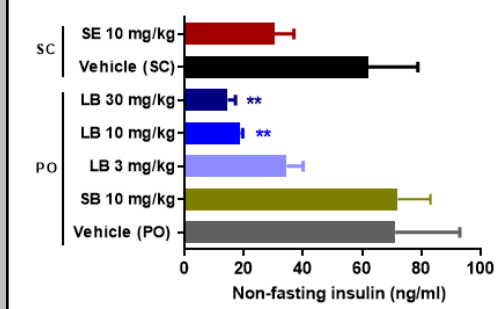
Food intake (Week 1)



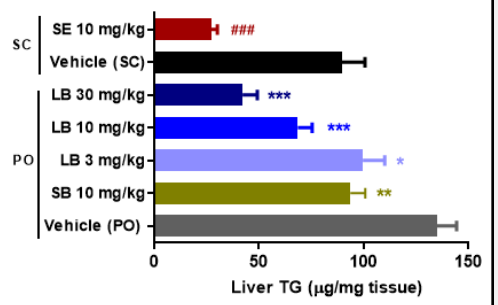
Glucose tolerance (Week 6)



Non-fasting insulin (Week 6)



Liver triglyceride (Week 7)



DIO mice were induced by feeding high fat diet from 5-weeks-old.

Mean±SEM, One-way ANOVA, post Dunnett's test (*p<0.05, **p<0.01, ***p<0.001),
Unpaired Student t-test, two-tailed ($^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001)

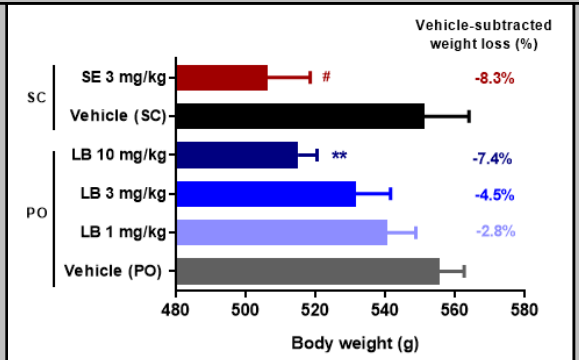
SB: Sibutramine, oral once a day
LB: LB54640 (LG Chem), oral small molecule, once a day
SE: in-class competitor, subcutaneously injected peptide, once a day

RESULTS (EFFICACY IN DIO RATS)

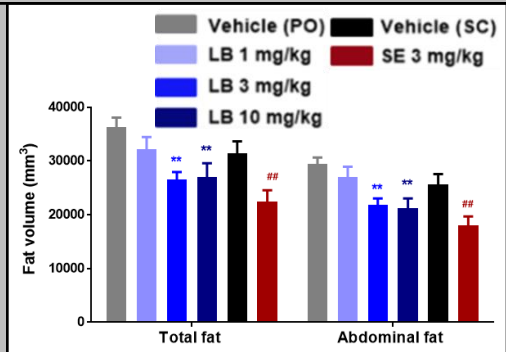
- Once daily administration of LB54640 resulted in significant reduction of body weight and food intake in DIO rats.

To evaluate the anti-obesity efficacy of repeated administration of LB54640 in DIO rats

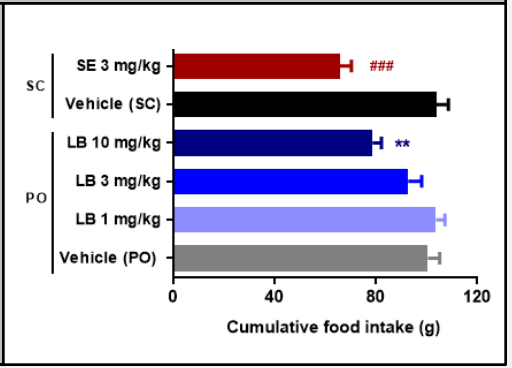
Body weight (Week 6)



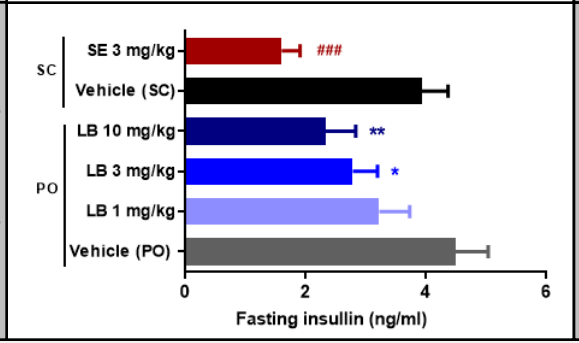
Fat volume (Week 6)



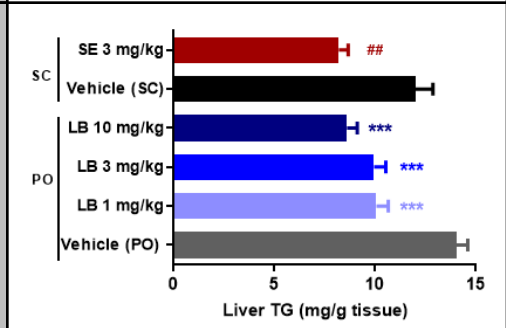
Food intake (Week 1)



Fasting insulin (Week 7)



Liver triglyceride (Week 7)



DIO rats were induced by feeding high fat diet from 5-weeks-old.

Mean±SEM, One-way ANOVA, post Dunnett's test (*p<0.05, **p<0.01, ***p<0.001),
Unpaired Student t-test, two-tailed (#p<0.05, ##p<0.01, ###p<0.001)

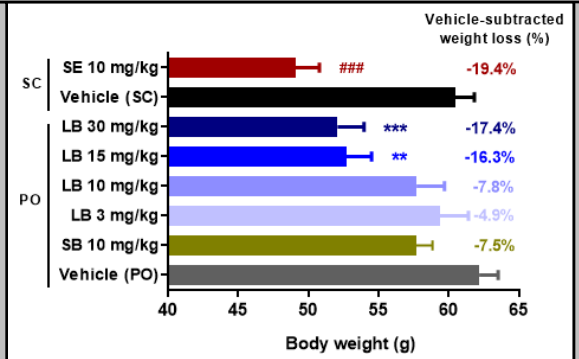
LB: LB54640 (LG Chem), oral small molecule, once a day
SE: in-class competitor, subcutaneously injected peptide, once a day

RESULTS (EFFICACY IN KK-A^{Y} MICE)

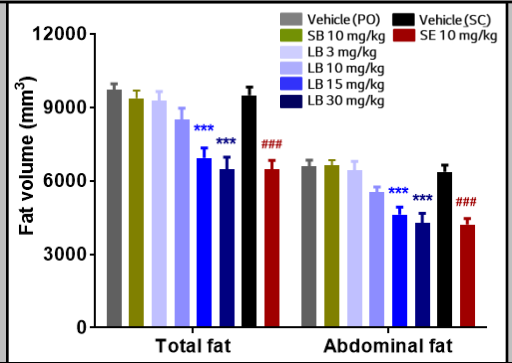
- Once daily administration of LB54640 resulted in weight loss and anorexic effect in KK-A^{y} mice fed with high fat diet.

To evaluate the anti-obesity efficacy of repeated administration of LB54640 in KK-A^{y} mice fed with high fat diet

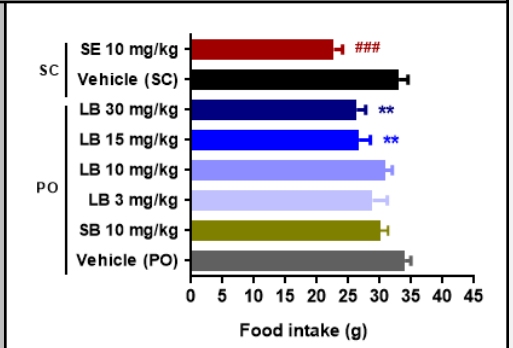
Body weight (Week 4)



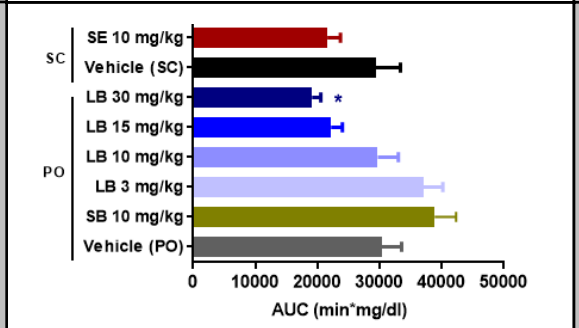
Fat volume (Week 4)



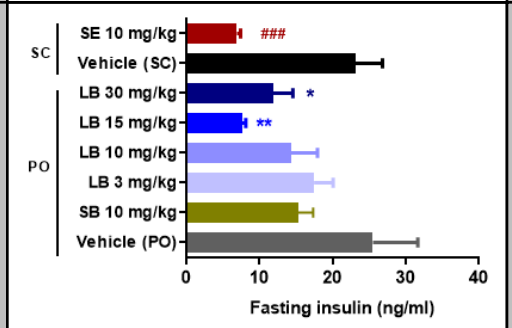
Food intake (Week 1)



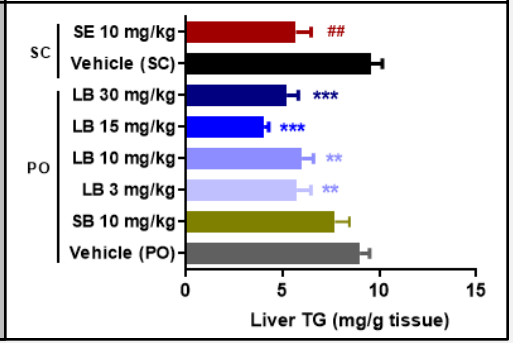
Glucose tolerance (Week 5)



Fasting insulin (Week 5)



Liver triglyceride (Week 5)



KK-A^{y} mice were fed with high fat diet from 7-weeks-old.

Mean±SEM, One-way ANOVA, post Dunnett's test (*p<0.05, **p<0.01, ***p<0.001),
Unpaired Student t-test, two-tailed ($^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001)

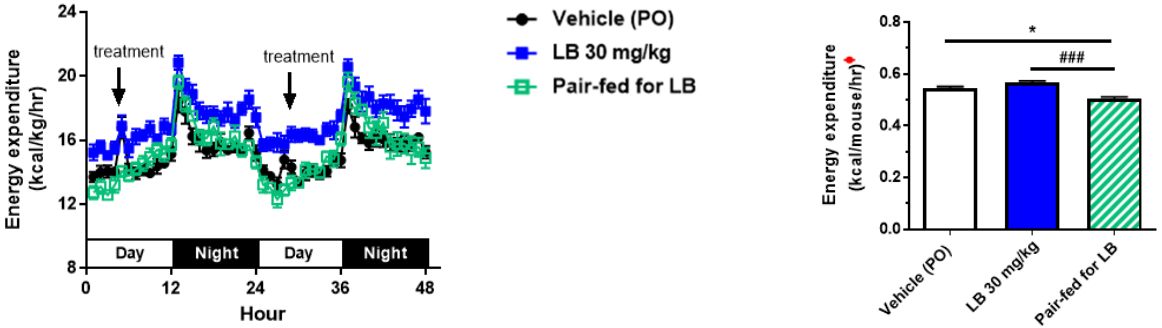
SB: Sibutramine, oral once a day
LB: LB54640 (LG Chem), oral small molecule, once a day
SE: in-class competitor, subcutaneously injected peptide, once a day

RESULTS (EFFECT ON ENERGY EXPENDITURE IN DIO MICE)

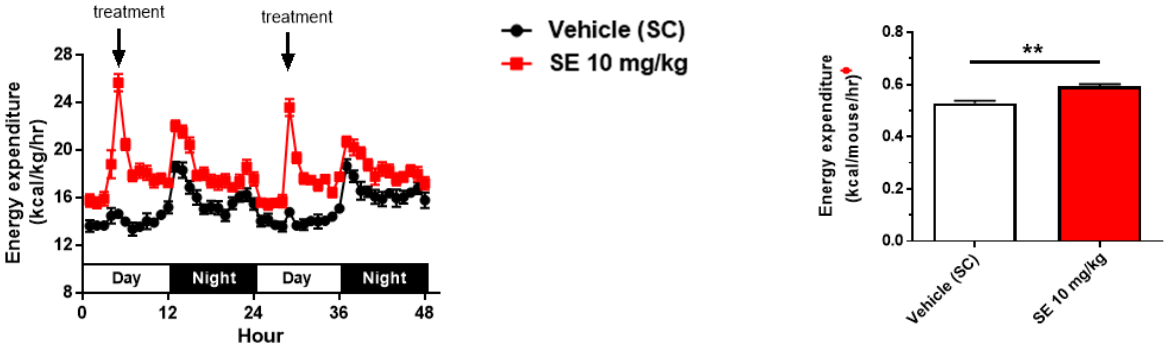
- LB54640 significantly increased energy expenditure, when compared to pair-fed group.

To evaluate the effect on energy expenditure of repeated administration of LB54640 in DIO mice

LB



SE



DIO mice were induced by feeding high-fat diet from 8-weeks-old.

LB: LB54640 (LG Chem), oral small molecule, once a day
SE: in-class competitor, subcutaneously injected peptide, once a day

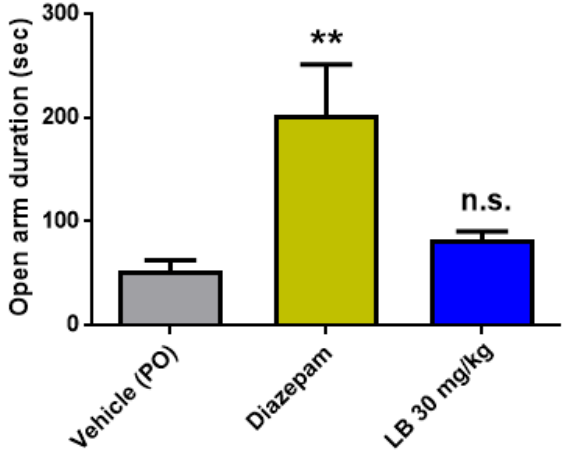
Φ Mean±SEM, ANCOVA, Bonferroni's analysis (*p<0.05, **p<0.01, ***p<0.001, #p<0.05, ##p<0.01, ###p<0.001)

RESULTS (EFFECT ON BEHAVIOR IN NORMAL MICE)

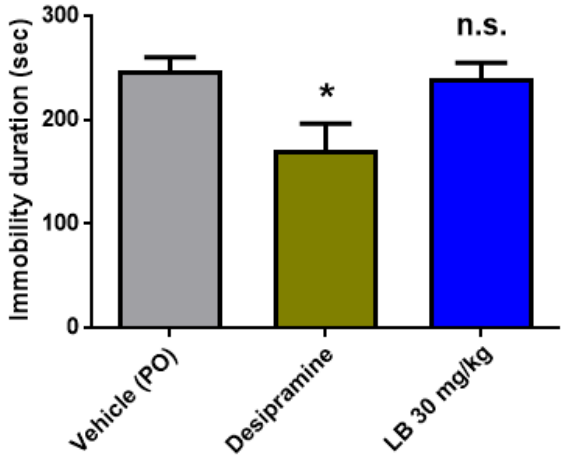
- LB54640 had no effect on behavior related to anxiety and depression.

To evaluate the effect of administration of LB54640 on anxiety or depression in normal mice

Elevated plus maze test



Tail suspension test



Diazepam: tranquilizer (positive control of elevated plus maze test)
Desipramine: antidepressant (positive control of tail suspension test)

LB: LB54640 (LG Chem), oral small molecule, once a day for 2 days

Mean±SEM, One-way ANOVA, post Dunnett's test (*p<0.05, **p<0.01, ***p<0.001),

Conclusion & Development timeline

Pharmacology

- LB54640 is a potent & selective MC4R agonist (in vitro)
- Significant body weight and food intake reduction in DIO rodents and genetically obese mice
- Anti-diabetic effect

ADME

- Orally available
- Brain exposure is close to plasma level supporting the pharmacologic effects
- No substantial food- or gender- related effects were observed
- No CYP inhibition or induction

Toxicology

- No safety concerns in 4W repeated dose toxicity studies and no skin & hair pigmentation
- No safety issue in the genotoxicity and safety pharmacology

LB54640

- ☑ First oral MC4R agonist
- ☑ Comparable efficacy compared to the in-class competitor
- ☑ Excellent safety profile with high selectivity to MC4R

Development Timeline

- IND submission for Phase 1 in Mar 2020 and approved in Apr 2020 (US FDA)
- Orphan drug designation under consideration
- NDA submission expected in 2026 (US FDA)