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Conference Report

2024 Biomedtracker Datamonitor Healthcare Post-ADA Report

August 2024

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Summary

The American Diabetes Association (ADA) 84th Scientific Sessions was held in Orlando on 21–24 June 2024 and featured the latest data from current therapeutic interventions and drug candidates for type 1 and type 2 diabetes, and obesity. Key data presented included the latest results of numerous glucagon-like peptide 1 (GLP-1)-based therapies, long-acting insulins, and disease-modifying therapeutics for type 1 diabetes. Preclinical and clinical research covering novel mechanisms of action was also presented, alongside data for innovative methods for improving drug delivery, including gene therapies.

This post-meeting report features commentary from our analysts on specific presentations. It also includes a compilation of data events added in conjunction with the meeting.

About the Author

Biomedtracker is an independent research service that offers proprietary clinical assessments and patient-based revenue forecasts of developmental drugs within a comprehensive and intuitive drug information database. Clients from the pharmaceutical, biotech, and investment industries rely on Biomedtracker for its insight on the likelihood of approval, commercial potential, and future data and regulatory catalysts for drugs within the competitive landscape of every important disease and indication. Over the last several years, Biomedtracker has become the leader in providing objective information alongside evidence based clinical assessments and investment research on pipeline drugs worldwide. For more information on getting direct access to Biomedtracker, please email clientservices@citeline.com.

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HFG1 for Diabetes Mellitus, Type I

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Endocrine
Lead Company:	HighField Biopharmaceuticals
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

HighField Biopharmaceuticals presented preclinical results for HGF1 in diabetic monkeys at the American Diabetes Association (ADA) 84th Scientific Sessions. An abstract entitled, "Preliminary Study of Efficacy and Duration of an mRNA-Based GLP-1R Agonist in Diabetic Monkeys," was presented at the meeting on June 22, 2024.

Context

HighField is planning to file a U.S. IND for HFG1 in the third quarter of 2024.

Design

Per the abstract, in order to characterize the HFG1 activities in vivo, five monkeys with naturally occurred diabetes (FPG≥9.69 mg/dl, HbA1c≥5.6%) were selected to receive one subcutaneous injection of LNPs of slightly variable compositions containing about 0.5-1.0mg mRNA. The monkeys were closely monitored for 60 days. Blood samples were collected at various time points and assayed in a GLP-1R/CRE Luciferase Reporter Cell system for GLP-1 equivalent activities.

Results

The monkeys experienced a reduced appetite for the first week following injection, after which their appetite returned to normal. Weight loss and A1C (HbA1c) reduction were significant.

Most Common Adverse Events

The monkeys were closely monitored following HFG1 injections. The monkeys showed no serious adverse effects.

Conclusion

Naturally occurred diabetic monkeys experienced weight loss and HbA1c level reduction during an assessment period of two months following a single injection with HFG1.

Comment

HFG1, a messenger ribonucleic acid (mRNA)-based GLP-1 receptor agonist designed for subcutaneous delivery, represents a novel approach aiming to mimic the body's natural production of GLP-1, therefore providing long-lasting GLP-1 agonism and a more convenient treatment alternative than the current weekly subcutaneous injection or daily oral formulations. In order to characterize HFG1 activity in vivo, five monkeys with diabetes (fasting plasma glucose [FPG] ≥9.69 mg/dl, HbA1c ≥5.6%) were selected to receive one subcutaneous injection of lipid nanoparticles of slightly variable compositions containing about 0.5-–1.0mg mRNA. By Day 56, an average reduction in body weight of 0.22kg was observed and the trend of HbA1c reduction was found to be statistically significant. No behavioral changes were observed except greatly reduced food uptake on the first few days after injection, a known effect of GLP-1 agonists. However, it should be noted that some time points were missing, and the sample size was small (n=5), so the observed HbA1c trend should be interpreted with caution. Despite these limitations, the data suggest HFG1 could be a promising potential treatment for diabetes and weight loss and should be evaluated in further studies to confirm efficacy and safety.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 1860-LB)
Investor Presentation 06/22/2024 (HighField, ADA Poster 1860-LB)
Business Wire 06/24/2024 (HighField)
Citeline Analysis

Mounjaro for Diabetes Mellitus, Type I

Event Date:	06/21/2024
Event Type:	Trial Data (Clinical Analysis)
Trial Name:	Phase IV – Real-World Studies
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	N/A
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Efficacy and Safety of Tirzepatide in Overweight (OW) and Obese (OB) Patients with Type 1 Diabetes (T1D)" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Today, most patients with T1D in the US are OW or OB, contributing to insulin resistance and suboptimal glucose control. The only FDA approved treatment for T1D, insulin, adversely affects weight. Tirzepatide is approved for managing T2D and causes weight loss. We assessed the use of tirzepatide in OW/OB subjects with T1D.

Methods

This was a retrospective single center real-world study in 62 adult OW/OB patients with T1D who were prescribed tirzepatide and followed for one year. The control group included 37 T1D patients (computer matched) with OW or OB who were not using any weight loss medications during the same period.

Results

The mean baseline age, duration of diabetes and HbA1c were similar in the 2 groups (Table 1a), while BMI and weight were higher in cases. There were significantly larger declines in BMI and weight in cases than controls across all time points (Table 1b). HbA1c decreased in cases as early as 3 months which was sustained throughout 1-year follow-up (Table 1 b). There was no reported increase in severe hypoglycemia or diabetic ketoacidosis throughout the study duration. Conclusions: In this pilot off-label use study, we conclude that tirzepatide facilitated an average 18.5% weight loss and improved glucose control in OW/OB patients with T1D. We strongly recommend a large prospective randomized control trial in OW/OB patients with T1D.

Conclusions

In this pilot off-label use study, we conclude that tirzepatide facilitated an average 18.5% weight loss and improved glucose control in OW/OB patients with T1D. We strongly recommend a large prospective randomized control trial in OW/OB patients with T1D.

Comment

A retrospective real-world study assessed off-label use of tizepatide in overweight and obese patients with type 1 diabetes. The mainstay of type 1 diabetes management, insulin, is associated with weight gain that can often be problematic given that a high proportion of these patients are overweight or obese. As such, the weight loss and metabolic benefits provided by GLP-1 agonists are of interest to this patient population. Evaluating 62 adult participants, significant changes in body weight (-18.5%) and HbA1c (-0.67%) were observed in the tirzepatide group compared to the control group (+1.2% and -0.02%, respectively) at 12 months. No increases in severe hypoglycemia or diabetic ketoacidosis were observed throughout the duration of the studies. Though limited by sample size and its retrospective nature, this study contributes to the body of evidence supporting further investigation of GLP-1 agonists for type 1 diabetes owing to their benefits in weight management and glycemic control.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 739-P)
Citeline Analysis

Awiqli for Diabetes Mellitus, Type I

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - ONWARDS-6
Market Group:	Endocrine
Lead Company:	Novo Nordisk A/S (NVO)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	74% (12% Below Avg.)
Average Approval:	86%

An abstract entitled "Efficacy and Safety Outcomes with Once-Weekly Insulin Icodec vs. Once-Daily Insulin Degludec in Type 1 Diabetes According to Glycemic Variability—ONWARDS 6 Post Hoc Analysis" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

ONWARDS 6 assessed the efficacy and safety of once-weekly insulin icodec (icodec) vs once-daily insulin degludec (degludec) in adults with type 1 diabetes (T1D). This post hoc analysis evaluated the impact of glycemic variability on efficacy and safety outcomes.

Methods

Outcomes were assessed across coefficient of variation (CV) subgroups (≤36% and >36%) based on CGM data from week 0-2.

Results

Estimated change in A1C with icodec vs degludec from baseline to week 26 was similar regardless of CV subgroup. In both arms, a numerically higher proportion of people with CV ≤36% vs CV >36% achieved A1C <7.0% at week 26. Estimated rate ratios (icodec/degludec) of combined clinically significant or severe hypoglycemia and CGM-based clinically significant hypoglycemic episodes were similar regardless of CV subgroup (Table). In both arms, hypoglycemia rates were numerically lower for people with CV ≤36% vs CV >36%. Time below range (<70 mg/dL and <54 mg/dL) during weeks 22-26 in the CV ≤36% subgroup was below recommended targets (<4% and <1%, respectively) and comparable between arms.

Conclusions

Similar to degludec, when used as part of a basal-bolus regimen in T1D, once-weekly icodec may offer a lower risk of hypoglycemia for people with low glycemic variability (CV ≤36%) than for those with high glycemic variability (CV >36%).

Comment

This post-hoc analysis of the ONWARDS 6 trial evaluated one of the mitigation measures proposed in insulin icodec's FDA advisory committee that ultimately voted against approval in type 1 diabetes. Specifically, whether restricting usage of insulin icodec to patients wearing diabetics wearing a continuous glucose monitoring device and with lower glycemic variability might mitigate the increased risk of hypoglycemia.

Results showed that insulin icodec offers a lower risk of hypoglycemia in patients with low glycemic variability (coefficient of variation [CoV] ≤36%) than with high glycemic variability (CoV >36%), with rates of 9.99 versus 25.41 events/patient-year, respectively. Though encouraging, it is of course expected that patients with better diabetic control (CoV ≤36%) have a lower risk of hypoglycemia, and similar trend was observed between the CoV subgroups for insulin degludec (5.74 vs. 15.07 events/patient-year, respectively). The analysis also showed that both the proportion of participants achieving HbA1C targets and the percentage of time in range (TIR) were numerically higher in the CoV ≤36% subgroup. Furthermore, time below range (TBR; <70mg/dL and <54mg/dL) during weeks 22–26 in the CoV ≤36% subgroup was below guideline recommended targets (<4% and <1%, respectively).

A major shortcoming with restricting usage to patients with low glycemic variability is that it is in fact the patients with poor diabetic control and inconsistent insulin usage who might benefit most from a weekly insulin like insulin icodec but are seemingly not be able to use it safely. It is also worth noting the typical caveats associated with post-hoc analyses and as such any interpretations should be taken with reservations. Consequently, given that the advisory committee agreed that additional trials would be required to validate the mitigation measures, we are keeping the LOA at 12% below average.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1882-LB)
Citeline Analysis

HFG1 for Diabetes Mellitus, Type II

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Endocrine
Lead Company:	HighField Biopharmaceuticals
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

HighField Biopharmaceuticals presented preclinical results for HGF1 in diabetic monkeys at the American Diabetes Association (ADA) 84th Scientific Sessions. An abstract entitled, "Preliminary Study of Efficacy and Duration of an mRNA-Based GLP-1R Agonist in Diabetic Monkeys," was presented at the meeting on June 22, 2024.

Context

HighField is planning to file a U.S. IND for HFG1 in the third quarter of 2024.

Design

Per the abstract, in order to characterize the HFG1 activities in vivo, five monkeys with naturally occurred diabetes (FPG≥9.69 mg/dl, HbA1c≥5.6%) were selected to receive one subcutaneous injection of LNPs of slightly variable compositions containing about 0.5-1.0mg mRNA. The monkeys were closely monitored for 60 days. Blood samples were collected at various time points and assayed in a GLP-1R/CRE Luciferase Reporter Cell system for GLP-1 equivalent activities.

Results

The monkeys experienced a reduced appetite for the first week following injection, after which their appetite returned to normal. Weight loss and A1C (HbA1c) reduction were significant.

Most Common Adverse Events

The monkeys were closely monitored following HFG1 injections. The monkeys showed no serious adverse effects.

Conclusion

Naturally occurred diabetic monkeys experienced weight loss and HbA1c level reduction during an assessment period of two months following a single injection with HFG1.

Comment

HFG1, a messenger ribonucleic acid (mRNA)-based GLP-1 receptor agonist designed for subcutaneous delivery,

represents a novel approach aiming to mimic the body's natural production and hopes to provide long-lasting GLP-1 agonism and therefore a more convenient treatment alternative than the current weekly subcutaneous injection or daily oral formulations. In order to characterize HFG1 activity in vivo, five monkeys with diabetes (fasting plasma glucose [FPG] ≥9.69 mg/dl, HbA1c ≥5.6%) were selected to receive one subcutaneous injection of lipid nanoparticles of slightly variable compositions containing about 0.5–1.0mg mRNA. By Day 56, an average reduction in body weight of 0.22kg was observed and the trend of HbA1c reduction was found to be statistically significant. No behavioral changes were observed except greatly reduced food uptake on the first few days after injection, a known effect of GLP-1 agonists. However, it should be noted that some time points were missing, and the sample size was small (n=5), so the observed HbA1c trend should be interpreted with caution. Despite these limitations, the data suggest HFG1 could be a promising potential treatment for diabetes and weight loss and should be evaluated in further studies to confirm efficacy and safety.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 1860-LB)
Investor Presentation 06/22/2024 (HighField, ADA Poster 1860-LB)
Business Wire 06/24/2024 (HighField)
Citeline Analysis

NA-931 for Diabetes Mellitus, Type II

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Endocrine
Lead Company:	Biomed Industries, Inc.
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	57% (Same As Avg.)
Average Approval:	57%

The abstract entitled “NA-931, a Novel Triple IGF-1/GLP-1/GIP Incretin Receptor Agonist Reduces Body Weight and Improves Metabolic Profile in DIO Mice” was presented at the American Diabetes Association (ADA) conference on June 22, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Design

Male diet-induced obese (DIO) mice were treated with daily subcutaneous injections of vehicle or one of novel triple IGF-1/GLP-1/GIP receptor agonists, NA-931, NA-932 and NA-933 (10 nmol/kg), for 14 days. Tirzepatide (10 nmol/ kg) as used as positive controls. Cohorts were then assessed for changes in BW, glucose, and lipids.

Results

Treatment with NA-931 Compounds resulted in reductions to BW (up to 26%, $p<0.0001$), plasma glucose, plasma triglycerides, (up to 23% and 34%, respectively, $p<0.003$ for each), and liver triglycerides (up to 46%, $p<0.05$) compared to vehicle treatment. Weight loss effects in cohorts treated with NA-931 Compounds were comparable to those observed in tirzepatide-treated animals. In addition, liver lipid reductions were numerically greater among animals treated with the NA-931Compounds.

Conclusion

NA-931 and its analogs produced significant reductions in BW in DIO mice. Effect sizes were comparable to those observed in the tirzepatide control group. The NA-931 Compounds have been shown to produce desirable changes to lipid profile, suggesting global cardiometabolic benefit, represent a promising therapeutic approach to metabolic disorders such as obesity, type 2 diabetes, and non-alcoholic steatohepatitis.

Comment

Biomed Industries' NA-931 is novel triple incretin receptor agonist, targeting GLP-1, GIP, and insulin-like growth factor 1 (IGF-1), which affects fuel metabolism and regulation of body composition. In obese murine models, daily subcutaneous injections of three NA-931 analogs administered over 14 days were compared with vehicle and tirzepatide as an active control. Significant body weight reductions of up to 26% were observed with the NA-931 analogs, as well as improvements in plasma glucose and triglyceride levels versus vehicle; hepatic fat was also markedly reduced. The observed weight loss effects across the NA931 analog cohorts were similar to tirzepatide. These findings support further development of NA-931 for type 2 diabetes, obesity, and MASH.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 2059-LB)
Citeline Analysis

KO-539 for Diabetes Mellitus, Type II

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Endocrine
Lead Company:	Kura Oncology, Inc. (KURA)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	N/A
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

Kura Oncology announced that preclinical data of Ziftomenib was presented in a poster entitled "The Menin Inhibitor Ziftomenib Induces Insulin Production and Improves Insulin Sensitivity in a Rat Model of Type 2 Diabetes Mellitus (T2DM)" at the American Diabetes Association's 84th Scientific Sessions on June 22, 2024.

Context

ziftomenib received breakthrough therapy designation for the treatment of relapsed/refractory (R/R) NPM1-mutant AML.

Design

Per the abstract, Zucker Diabetic Fatty rats were used to assess the antidiabetic activity of ziftomenib dosed orally once daily for 27 days.

Results

Ziftomenib demonstrated good levels of glycemic control in preclinical in vivo models, including reduced fasting blood glucose levels and %HbA1C within 27 days as well as consistent improvement in both insulin sensitivity and insulin production. The data show that the effects of ziftomenib were maintained following dose discontinuation, suggesting restoration of beta-cell mass. A decline in pancreatic beta-cell function and/or mass has been defined as a key contributing factor to disease progression in type 2 diabetes. Notably, in human islet microtissues originating from two donor samples, ziftomenib induced beta-cell proliferation while non-beta-cell proliferation was not detectable, demonstrating menin is a viable therapeutic target for beta-cell mass specific expansion.

Per the abstract, Ziftomenib rapidly reduced fasting blood glucose (FBG) levels, with normalization of FBG levels observed in most animals within 2 weeks. Ziftomenib also progressively reduced %HbA1C by an average of 1.49% by week 4. Oral glucose tolerance tests demonstrated that ziftomenib-treated animals achieved significantly improved postprandial glucose control ($P<0.0001$). Ziftomenib induced a reduction in HOMA-IR within 1 week, suggesting that one of the effects of menin inhibition is acute sensitization of the animals to insulin. In addition, fasting insulin and c-peptide levels demonstrated that ziftomenib significantly stimulated insulin production at week 3-4.

Conclusion

Ziftomenib induces insulin production, improves insulin sensitivity and reduces insulin resistance in preclinical model of type 2 diabetes.

Comment

In early-stage development for type 2 diabetes, ziftomenib is a potent and selective menin inhibitor originally in development for acute leukemias. As genetic menin loss is associated with insulinemia due to upregulated pancreatic beta-cell proliferation, menin inhibition represents a viable novel treatment approach. A preclinical study in diabetic rats showed that ziftomenib significantly reduced fasting blood glucose and HbA1c within 27 days of treatment. Indicative of substantial improvements in beta-cell function, ziftomenib demonstrated significant increases in serum insulin and C-peptide levels. Moreover, efficacy was maintained after dosing discontinuation, which could be attributed to pancreatic beta-cell mass restoration. With proof of concept achieved in an animal model, ziftomenib and second-generation menin inhibitors have the potential to be novel disease-modifying treatment options for type 2 diabetes.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 845-P)
American Diabetes Association (ADA) 06/22/2024 (Poster 845-P)
Globe Newswire 06/24/2024 (KURA)
Citeline Analysis

Mounjaro for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase IIIb - SURPASS-6 (vs. Insulin Lispro)
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Near-Normoglycemia and Insulin Regression Induced by Tirzepatide in Basal Insulin–Treated Type 2 Diabetes" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

In the SURPASS-6 trial, addition of tirzepatide (TZP) to basal insulin glargine U100 in participants with inadequately controlled long-standing type 2 diabetes (T2D), substantially improved HbA1c and body weight. We evaluated degrees of insulin dose reductions and the efficacy and safety of TZP based on residual insulin use at Week 52.

Methods

“Insulin regressor” was defined as basal insulin discontinuation or <10 IU/day, and “insulin non-regressor” as ≥10 IU/day, at 52 weeks. Included only participants receiving TZP at Week 52 (≥75% compliance) without rescue medication. Efficacy analyses used a mixed model for repeated measures.

Results

Overall, 145 and 496 TZP-treated participants were included in the insulin regressor vs. insulin non-regressor groups, respectively. At baseline, mean age was 58.4 vs. 58.2 years, and median basal insulin dose was 40.0 vs. 48.0 IU/day. From baseline to Week 52 in the insulin regressor and insulin non-regressor groups, respectively, mean HbA1c of 8.5% and 8.9% was reduced to 5.9% and 6.7%, while weight was substantially reduced by 16 kg and 8 kg. Clinically significant hypoglycemia was also less frequent in the insulin regressor group (Table).

Conclusions

In basal insulin-treated T2D, participants who regressed on insulin use also achieved near-normoglycemia and substantial weight loss.

Comment

A new analysis of the SURPASS-6 trial assessed the impact of degrees of insulin dose reductions and the efficacy and safety of tirzepatide based on residual insulin use in participants with inadequately controlled long-standing type 2 diabetes. Insulin regressor and non-regressor subgroups were defined as basal insulin discontinuation or <10 IU/day, and as ≥10 IU/day, at 52 weeks, respectively. The trial identified 145 insulin regressors and 496 non-regressors in patients treated with tirzepatide. Insulin regressors achieved greater HbA1c reductions (-2.6% vs. -2.2%) and weight loss (-16.1kg vs. -7.7.kg) at Week 52 compared to baseline than non-regressors. Insulin regressors also achieved near normoglycemia at Week 52, specifically HbA1c was reduced from 8.5% to 5.9%, where normoglycemia is typically defined as HbA1c <5.7%. In summary, the potential to reduce or even eliminate insulin dependence and therefore providing major benefits in terms of convenience and reducing the side effects of long-term insulin use, coupled with exceptional glycemic control and substantial weight loss, makes tirzepatide an even more attractive treatment option across the diabetes spectrum.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 757-P)
Citeline Analysis

Mounjaro for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data (Clinical Analysis)
Trial Name:	Phase IV – Real-World Studies
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Real-World Effectiveness among Patients with Type 2 Diabetes (T2D) Initiating Tirzepatide (TZP)" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

TZP is a once weekly glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist (RA) approved in the US for treatment of T2D and obesity. The goal of this single-cohort retrospective study was to assess effectiveness of TZP in patients (pts) with T2D in a US commercially insured population.

Methods

Adult pts diagnosed with T2D, initiating TZP between 5/2022 and 8/2023, with ≥1 A1C result around initiation and another 6 months post-initiation were identified from the Healthcare Integrated Research Database (HIRD®). Baseline demographics, A1C and weight outcomes at 6-month follow-up for overall cohort and stratified by prior GLP-1 RA use and baseline A1C (<7% vs ≥7%) were described.

Results

Among 2,247 identified pts: mean age 54 years, 58% female, 46% no prior GLP-1 RA use, 59% A1C ≥7%, 61% had overweight/obesity. At 6-month follow up, mean pre-post change in A1C was -1.0% in the overall cohort, -1.4% among pts with baseline A1C ≥7%, and -1.3% in those without prior GLP-1 RA use. Mean change in weight was -6.3 kgs for overall cohort, -5.8 kgs in pts with baseline A1C ≥7%, and -8.1 kgs in those without prior GLP-1 RA use. Further outcomes are summarized in Table 1.

Conclusions

At 6-month follow up, pts initiating TZP in the real world showed reductions in A1C and weight, with greater A1C decreases observed among pts with no prior GLP-1 RA use or with baseline A1C ≥7%.

Comment

A retrospective study of 2,247 patients in the US confirmed tirzepatide's effectiveness in reducing HbA1c and weight in a real-world setting. At six-month follow-up, the mean changes in HbA1c in the overall cohort, among patients with baseline A1C ≥7%, and in those without prior GLP-1 agonist use, were -1.0%, -1.4%, and -1.3%, respectively, and changes in weight for the subgroups were -6.3kg, -5.8kg, and -8.1kg, respectively. These data complement previous findings for tirzepatide and build a stronger case for its effectiveness in managing type 2 diabetes in a broad and diverse patient population.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 738-P)
Citeline Analysis

Mounjaro for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - SURPASS-5 (w/Basal Insulin) Phase IIIb - SURPASS-6 (vs. Insulin Lispro)
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Tirzepatide as an Add-on for Participants with Inadequate Glycemic Control Using Basal Insulin—Pooled Subgroup Analysis of SURPASS-5 and -6" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

In SURPASS-5 and -6, tirzepatide (TZP) added to basal insulin significantly improved glycemic control vs. comparators in participants with type 2 diabetes (T2D) with inadequate glycemic control (HbA1c [%] 7.0-10.5 and 7.5-11.0, respectively). Analyses evaluated key clinical parameters at Week 40 within participant subgroups.

Methods

A post hoc analysis including TZP-treated participants using titrated insulin glargine (100 IU/mL) with or without metformin by subgroup: age (<65, ≥65 years), T2D duration (<10, ≥10 years), and baseline (BL) HbA1c (≤8.5%, >8.5%). Data were pooled for SURPASS-5 and -6 up to Week 40.

Results

Overall, 1072 participants were included. At BL, mean age was 59.3 years; 583 (54.4%) were female; mean T2D duration was 13.5 years; mean weight was 92.3 kg, mean HbA1c was 8.6%, and median insulin dose was 42 IU/day. For all subgroups, TZP treatment significantly reduced HbA1c and weight from BL to Week 40 without heterogeneity. Incidence of clinically significant hypoglycemia was numerically higher for participants in HbA1c >8.5% and T2D duration ≥10 years subgroups (Table).

Conclusions

In this post hoc analysis of people with T2D and inadequate glycemic control with basal insulin with or without metformin, participants treated with TZP experienced significantly improved HbA1c and weight across different subgroups.

Comment

A pooled subgroup analysis of the SURPASS-5 and SURPASS-6 trials adds to the body of evidence supporting tirzepatide's use across the diabetes spectrum. The analysis included type 2 diabetes patients with inadequate glycemic control who were treated with tirzepatide and using basal insulin with or without metformin. Findings show that tirzepatide elicited statistically significant benefits on HbA1c regardless of age, duration of type 2 diabetes, or baseline HbA1c level. The incidence of clinically significant hypoglycemia was numerically higher for participants in HbA1c >8.5% and disease duration ≥10 years subgroups, which may be explained by the insulin-sensitizing effects of tirzepatide and patients in these subgroups may have been on higher insulin doses due to their disease severity, thus leading to a higher risk of hypoglycemia. These findings show that tirzepatide has consistent efficacy across a range of different patient subgroups in terms of glycemic control and weight loss.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 749-P)
Citeline Analysis

Mounjaro for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data (Clinical Analysis)
Trial Name:	Phase IV – Real-World Studies
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Tirzepatide—Efficacy, Safety, and Satisfaction in Real World Type 2 Diabetes Application in Japan" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

To analyze the efficacy and safety of Tirzepatide (Tir) in improving blood glucose control in clinical practice.

Methods

People with type 2 diabetes who received Tir for 8 months from April 2023, were retrospectively evaluated for changes in HbA1c and given a satisfaction survey. Of the 94 people (49 males, age 63±15 years, BMI 25.3±6.7, starting HbA1c 8.1±1.7 %, 25 people on insulin), 2 were on Tir 10 mg, 3 on 7.5 mg, and the rest on ≤5 mg.

Results

HbA1c decreased on average 1.7±1.7 % and 8 were weaned from insulin therapy. Eight had no change in HbA1c or a worsening of around 0.55% on average due to oral medications or insulin dose reductions. Ten ceased Tir therapy, 3 of which achieved effective target HbA1c and were weaned at their request, 1 had large weight loss, 1 experienced hypoglycemia due to combined use with insulin and preferred to discontinue Tir rather than reduce insulin dosage, 5 experienced gastrointestinal symptoms, and 1 changed to a GLP1 formulation due to infrequent hospital visits. In one case, sleep apnea improved, and one person with Alzheimer's disease and uncontrolled food intake achieved a healthy level of food intake. One person with Prader-Willi syndrome could not reach target HbA1c due to dietary restriction limitations caused by possible insufficient Tir dosage. In the survey, 80% were satisfied, 50% would recommend the treatment to others due to superior overall results and weight loss, and 50 % stipulated unwillingness in recommending it to others, although satisfied, due to uncertainty over the effectiveness in others. Two percent were dissatisfied. Eighty percent of respondents indicated continued treatment. In comparison to their previous therapies, 90% felt healthier and more active, that Tir was a better fit and didn't place a burden on their daily lives, and that it was successful in controlling body weight.

Conclusions

Further observation is needed.

Comment

A real-world analysis retrospectively assessed the efficacy and safety of tirzepatide in improving blood glucose control as well as treatment satisfaction in clinical practice in Japan. Though data were from a relatively small sample size, HbA1c reductions were comparable to those observed in RCTs, confirming effectiveness in a real-world setting. Furthermore, the majority of patients were satisfied with their tirzepatide treatment and indicated desire to continue treatment. Despite the study only followed patients for 8 months and more long-term real-world studies would be of value, these results are promising for tirzepatide's effectiveness and treatment satisfaction in the Japanese population.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 12-PUB)
Citeline Analysis

Efsitora alfa for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase I - I8H-MC-BDCI (Germany)
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	61% (4% Above Avg.)
Average Approval:	57%

An abstract entitled "Effects of Insulin Efsitora Alfa (Efsitora) on Frequency and Severity of Hypoglycemia (Hypo) Under Conditions of Increased Hypo Risk Compared with Glargine in Type 2 Diabetes (T2D)" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Efsitora is an insulin receptor agonist designed to have a flat pharmacokinetic profile and long half-life enabling weekly dosing. While these features may provide stable glucose levels, their impact on hypo risk is less clear. A phase 1 study was conducted to assess hypo risk using controlled, experimental conditions that mimic hypo risk situations that may be encountered in daily life.

Methods

This single-site, open-label, 2-period, fixed-sequence (glargine-efsitora) study was conducted in 54 participants with T2D previously on basal insulin (BMI 21.8-39.7 kg/m2, HbA1c 6.5-9.4%). After titration to stable fasting glucose (FG) with glargine or efsitora, the incidence of hypo was assessed during 3 test conditions: prolonged fasting 24-hrs (PF), PF with exercise (EX), and after receiving a double dose (DD) of study insulin.

Results

Mean FG at start of tests was 6 mg/dL lower with PF and EX and 10 mg/dL lower with DD in the efsitora group compared to glargine. Incidence of Level 1 hypo (≥54 to <70 mg/dL) was not significantly different under any test condition: incidence efsitora vs glargine, difference in proportion (95%CI) for PF: 44.7 vs 42.6%, 2.1 (-17.2, 21.4); EX: 65.9 vs 50.0%, 15.9 (-3.0, 34.8); DD: 68.1 vs 61.7%, 6.4 (-12.8, 25.6). Level 1 hypo resolved spontaneously or after 15g oral glucose. Level 2 (<54 mg/dL) was infrequent in both treatments and all test conditions. No severe hypo occurred in this study. Mean nadir glucose for hypo was similar between treatments and test conditions ranging from 62.8-66.3 mg/dL. Duration of hypo events was also similar between treatments ranging from 76.6 to 115.2 mins depending on the test conditi

Conclusions

Once weekly efsitora did not increase the incidence, duration, or severity of hypo compared to once daily glargine during periods of provocation in patients with T2D.

Comment

Results from the Phase I study show efsitora alfa did not significantly increase the incidence, duration, or severity of hypoglycemia compared to insulin glargine, though rates were slightly numerically higher. The risk of hypoglycemia was evaluated using conditions that mimic hypoglycemia risk situations that may be encountered in daily life. The incidence of hypoglycemia was evaluated during three test conditions: prolonged fasting for 24 hours, prolonged fasting with exercise, and after receiving a double dose of study insulin. Specifically, level 2 hypoglycemia was infrequent in both treatments and all test conditions, and no severe hypoglycemia was observed in the study. By demonstrating a comparable hypoglycemia risk profile to insulin glargine under simulated challenging real-world conditions, efsitora alfa has confirmed its favorable safety profile as seen in other clinical studies conducted to date. Though only from 54 participants and thus requiring validation by larger long-term studies, these results are promising for efsitora alfa considering the troubles faced by competitor Novo Nordisk's insulin icodec and its risk of hypoglycemia.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 818-P)
Citeline Analysis

ATR-258 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Endocrine
Lead Company:	Atrogi
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "ATR-258 Is a Precision Modulator of ß2-AR Signaling That Improves Glucose Homeostasis and Is Safe in Humans" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Stimulation of β2-adrenergic receptors (β2-AR) in skeletal muscle improves glucose uptake capacity and is a promising avenue in the treatment of type 2 diabetes (T2D). To circumvent common β2-AR-associated cardiovascular side-effects through cAMP activation, we have developed a novel β2-AR agonist, ATR-258, with low cAMP induction but improved glucose tolerance and insulin sensitivity in preclinical models. Here we present preclinical efficacy data and phase 1 safety data for our candidate drug ATR-258.

Methods

We have used various in vitro models to analyze the functional characteristics of ATR-258. These include receptor selectivity, downstream signaling profiles, cAMP induction and glucose uptake. We assessed the in vivo effects of ATR-258 on glucose tolerance and insulin sensitivity in diet-induced obese C57BL/6 mice and diabetic Goto-Kakizaki rats. To test safety in humans, we performed single and multiple ascending dose studies in a total of 46 healthy male volunteers. In a third cohort, 23 male patients with T2D received either placebo (n = 8) or 2.5 mg ATR-258 (n = 15) once daily for 28 days. Safety profiles, PK, and PD variables such as HbA1c and glucose tolerance were measured.

Results

ATR-258 displayed limited cAMP induction and no promotion of β-arrestin recruitment or receptor desensitization, but a maintained ability to induce glucose uptake compared to classical β2-AR agonists in vitro. ATR-258 improved glucose tolerance and insulin sensitivity in a dose-dependent manner in mouse and rat models of obesity and diabetes. Our first-in-human phase 1 data showed that ATR-258 is safe and well-tolerated in healthy volunteers and T2D patients.

Conclusions

ATR-258 is a β2-AR agonist with a preferential signaling and safety profile resulting in beneficial effects on glucose

homeostasis in preclinical models and a promising safety profile in humans. ATR-258 could lead the way of a new class of adrenergic agonists to treat T2D.

Comment

ATR-258 is a β2-adrenergic receptor agonist that is being investigated as a potential treatment for type 2 diabetes. β2-adrenergic receptor agonists are typically used to treat asthma and other pulmonary disorders as their effects on smooth muscle cause causes dilation of the bronchial passages, however, stimulation of β2-adrenergic receptors in skeletal muscle improves glucose uptake capacity is therefore a promising avenue for treating type 2 diabetes

Preclinical functional characteristics and efficacy were evaluated using various *in vitro* models and *in vivo* in diet-induced obese mice and diabetic rats. Functional outcomes included receptor selectivity, downstream signaling profiles, cAMP induction, and glucose uptake. Efficacy outcomes included glucose tolerance and insulin sensitivity. To test safety in humans, a first-in-human Phase I study was conducted involving single and multiple ascending doses in a total of 46 healthy male volunteers, while a third cohort of patients with type 2 diabetes were given placebo or ATR-258 once daily for 28 days. Preclinical data showed that ATR-258 displayed limited cAMP induction but maintained the ability to induce glucose uptake compared to classical β2-AR agonists *in vitro*. ATR-258 also improved glucose tolerance and insulin sensitivity in a dose-dependent manner in mouse and rat models of obesity and diabetes. Phase I results showed ATR-258 to be safe and well tolerated in both healthy patients and type 2 diabetics.

In summary, these results support the further evaluation of ATR-258 as a potential treatment for type 2 diabetes. Differentiated from currently available diabetes treatments, which target different aspects of glucose control, ATR-258 could be an innovative treatment approach for type 2 diabetes.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1883-LB)
Citeline Analysis

ZT002 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Top-Line Results (Clinical Analysis)
Trial Name:	Phase I - SAD
Market Group:	Endocrine
Lead Company:	Beijing QL Biopharmaceutical Co.,Ltd
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a Novel Ultra-Long-Acting GLP-1 Receptor Agonist (ZT002) in Healthy Subjects" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

ZT002, a novel ultra-long-acting GLP-1RA, is designed for monthly or biweekly subcutaneous administration and has non-inferior efficacies and a safety profile to semaglutide. Preclinical pharmacokinetics (PK) studies in multiple species (mouse, rat, minipig, monkey) demonstrated ZT002 had a 2-4 fold longer half-life than semaglutide. This first-in-human study assessed the safety, tolerability, PK, and pharmacodynamics (PD) of single ascending doses (SAD) of ZT002 in healthy subjects.

Methods

This phase 1, randomized, double-blind, placebo-controlled, SAD trial was conducted in Australia. Overtly healthy adults 18-55 years with the body mass index of 22.0-35.0 kg/m2 were randomized (6:2) to receive ZT002 (0.03, 0.09, 0.13 and 0.26 mg/kg) or placebo.

Results

A total of 32 subjects [N=20 (male)/12 (female); median age=28 years; median BMI=26.7 kg/m2)] participated in the SAD trial. There were no serious adverse events, deaths or treatment-emergent adverse events (TEAEs) that led to withdrawal. The most common TEAEs related to the study drug were gastrointestinal (nausea and vomiting), and the majority were considered mild and transient. The PK profile was dose-proportional over the dose range with a mean half-life of 260-273 hours, supporting a monthly or biweekly injection. Weight loss from baseline at Day 15 was dose-responsive across the 4 cohorts, and the mean reduction in body weight (BW) from baseline on Day 14 was 2.01 kg in subjects with 0.26mg/kg ZT002 and clinically meaningful weight reduction, in comparison to the placebo, was maintained up to Day 71.

Conclusions

This SAD trial of ZT002 demonstrated acceptable safety, tolerability profile, and superior PK profiles. Significant reductions in BW were observed in healthy subjects. Further clinical development of ZT002 as a monthly or biweekly injectable therapy for obesity and type 2 diabetes mellitus (T2DM) is underway.

Comment

ZT002 is an ultra-long-acting GLP-1 receptor agonist under development as a once-monthly subcutaneous administration based on the addition of fatty acids at each end of the molecule extending half-life due to increased albumin-binding affinity. In this single ascending dose Phase I study involving 32 healthy volunteers, doses of 0.03mg/kg up to 0.26mg/kg were evaluated. There were no withdrawals following randomization, the majority of AEs were characterized as mild, and there were no serious AEs associated with the active treatment.GI AEs were the most common and were consistent with the GLP-1 agonist class. A mean half-life of up to 273 hours was confirmed in humans, much longer than currently marketed products.

Dose-dependent weight loss was demonstrated out to 71 days (10 weeks) after dosing, with the top dose showing a statistically significant difference versus placebo. Discussion questions included when the GI AEs occurred for the highest doses, which might have contributed to weight loss, but it was explained that the AEs resolved after three days. Also, it was purported that the half-life suggests dosing every two weeks rather than monthly dosing, which if adopted might lead to inconsistent drug levels. However, the presenter, Yuanyuan Zhang, suggested that other pharmacokinetic factors can have an impact, particularly in obese patients, which might allow for the longer dosing interval. Concerns regarding dose accumulation were raised, but this will need to be checked in multiple ascending dose studies.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 119-OR)
Citeline Analysis

Retatrutide for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - vs. Dulaglutide
Market Group:	Endocrine
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	3%
Likelihood of Approval:	60% (3% Above Avg.)
Average Approval:	57%

An abstract entitled "Retatrutide, an Agonist of GIP, GLP-1, and Glucagon Receptors, Improves Markers of Pancreatic Beta-Cell Function and Insulin Sensitivity" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Retatrutide (RETA), an agonist of GIP, GLP-1 and glucagon receptors, significantly reduced HbA1c up to 2.2% in T2D and body weight up to 17% in T2D at wk 36 and 24% in obesity without T2D (OB) at wk 48 in Ph2 trials.

Methods

To explore mechanisms by which RETA improved glycemic control, we assessed markers of beta-cell function and insulin sensitivity. Mixed models for repeated measures evaluated fasting biomarkers from two Ph2 double-blind randomized placebo-controlled trials: in T2D (281 subjects, 36-wks) and in OB (338 subjects, 48-wks).

Results

Homeostatic model assessment (HOMA2)-IR index (insulin), a measure of insulin resistance, decreased over time from baseline with RETA 12 mg reaching reductions of 39% in T2D at 36 wks and 52% in OB at 48 wks. Adiponectin, a marker of insulin sensitivity, increased with RETA from baseline up to 52% in T2D and up to 70% in OB, ($p<0.001$). HOMA2-B index (C-peptide), a marker of beta-cell function, rapidly increased with RETA up to 88% from baseline in T2D but did not significantly increase in OB. Proinsulin and proinsulin/C-peptide ratios, measures of beta-cell stress and dysfunction, decreased from baseline with RETA, by up to 71% and 62%, respectively, in T2D ($p<0.001$).

Conclusions

In conclusion, RETA improved markers of beta-cell function in T2D and markers of insulin sensitivity in T2D and OB.

Comment

Two Phase II double-blind, randomized, placebo-controlled trials assessed retatrutide in both patients with type 2 diabetes and overweight/obesity. The Phase II diabetes study enrolled 281 type 2 diabetes patients with HbA1c between 7% and 10.5% who had been treated with diet and exercise alone or with a stable dose of metformin for at least three months prior to screening. The primary outcome was change in HbA1c from baseline, and key secondary endpoints included change in body weight and change in fasting blood glucose. The other Phase II study enrolled 338 obese or overweight participants and utilized a primary endpoint of mean change in body weight from randomization to Week 24. Data from the Phase II trials showed that retatrutide significantly reduced HbA1c by up to 2.2% and body weight by up to 17% in type 2 diabetes patients at Week 36, and reduced body weight by 24% in obesity patients without type 2 diabetes at Week 48.

The analysis assessed markers of beta-cell function and insulin sensitivity to elucidate the mechanisms by which retatrutide improves glycemic control. Homeostatic model assessment (HOMA) 2-IR index, a marker of insulin resistance, decreased from baseline, with the highest dose (12mg) achieving the largest reductions. Specifically, retatrutide (12mg) produced reductions of 39% compared to 22% for placebo in type 2 diabetics at 36 weeks, and 52% compared to 12% in obese patients at 48 weeks. Assessment of beta-cell function through C-peptide showed that retatrutide increased HOMA2-B index by up to 88% from baseline in type 2 diabetes, but did not show a significant increase in obesity.

Overall, retatrutide appears to improve beta-cell function and insulin sensitivity in patients with type 2 diabetes and obesity. A question was asked about the correlation between weight loss and the insulin resistance reported, with a reply from Dr. Melissa Thomas that the linear pattern had not been explored but glycemic improvements occurred quickly, although the insulin sensitivity appeared to have a longer time course and further research was needed. Evidence indicates retatrutide improves markers of beta-cell function in type 2 diabetes and markers of insulin sensitivity in type 2 diabetes and obesity, suggesting that GIP/GLP-1/glucagon triple agonism is a potential valuable treatment option. Importantly, as glucagon can interfere with insulin action, these improvements in beta-cell function and insulin sensitivity may offset any interference and as such are playing a role in retatrutide's ability to produce exceptional glycemic control.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 266-OR)
Citeline Analysis

GLY-200 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - Double Blind Study
Market Group:	Endocrine
Lead Company:	Glyscend Therapeutics, Inc.
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	3%
Likelihood of Approval:	18% (3% Above Avg.)
Average Approval:	15%

An abstract entitled "GLY-200 (Oral Pharmacologic Duodenal Exclusion Drug) Decreases Appetite, Increases Satiation, and Reduces Food Intake in Patients with Type 2 Diabetes" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

GLY-200 is an investigational oral non-absorbed polymeric drug designed to bind to and enhance the barrier function of gastrointestinal mucus as a non-invasive alternative to metabolic surgery and duodenal exclusion devices. In healthy volunteers, GLY-200 lowered glucose and increased GLP-1, PYY, and bile acids, indicating pharmacologic effects of duodenal targeting. This 14-day Ph2 study in patients with type 2 diabetes (T2D) evaluated the safety, tolerability, and pharmacodynamic effects of GLY-200 and showed reduced glucose and progressive body weight loss at the 2.0 g GLY-200 dose.

Methods

Randomized, double-blind, placebo (PBO)-controlled inpatient study with 14 days BID dosing of 2.0 g GLY-200 [N=13, BMI 31.8 ± 4.1 kg/m2, baseline (BL) HbA1c 7.2 ± 0.7%] and PBO (N=12, BMI 31.7 ± 3.2 kg/m2, BL HbA1c 7.2 ± 0.7%). On Day -1, 1, and 13, food intake and appetite VAS were assessed at standardized breakfasts and ad libitum dinners. Categorical food intake (0-25%, 26-50%, 51-75%, 76-100% consumed) was assessed at all other inpatient meals.

Results

GLY-200 appeared safe and well-tolerated with most AEs being GI-related. With 2.0 g GLY-200, a greater overall appetite suppression (OAS) score was seen immediately post-meal (↑35.9%, p=0.004) and 60 min after the standardized breakfast (↑28.7, p=0.02) vs PBO. Before the ad libitum dinner, the OAS score was ↑28% (p=0.004) in 2.0 g GLY-200 subjects vs PBO. When allowed to eat as much as desired, 2.0 g GLY-200 subjects had significantly lower food intake (↓17.0%, p=0.026). During non-standardized inpatient meals, an average of 22.1%, 19.5%, and 28% of 2.0 g GLY-200 subjects consumed ≤75% of breakfast, lunch, and dinner, respectively, vs 0%, 4.8% and 6.8% of PBO subjects.

Conclusions

Increased satiation/satiety, decreased feeling of hunger, and reduced food intake, in part, explains the body weight loss observed with 2.0 g GLY-200 treatment, consistent with the intended mechanism of the drug.

Comment

Designed to mimic the effect of metabolic surgery, GLY-200 is a first-in-class gut-restricted polymer that enhances the mucus natural barrier to establish a pharmacological duodenal exclusion. Non-surgical duodenal exclusion offers several advantages over traditional metabolic surgery including adjustable effects, reversibility, lower overall cost and reduced discomfort and pain. Phase II clinical data for GLY-200 are consistent with the intended mechanism, results from 51 subjects with type 2 diabetes demonstrated clinically meaningful reductions in fasting and postprandial glucose, fasting lipids, body weight, food intake, and appetite versus placebo. GLY-200 doses varying from 0.5g up to 2.0g or placebo were administered two times a day for 14 days. GLY-200 also appeared safe and well tolerated, with most AEs being GI-related. These data are consistent with the anti-diabetic and anti-obesity effects of other more invasive approaches to duodenal exclusion and support further clinical development. As such, given the success of this Phase II trial in achieving proof-of-concept, we are raising the LOA by 3%.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 864-P)
Citeline Analysis

HS-20094 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Top-Line Results (Clinical Analysis)
Trial Name:	Phase II - HS-20094-201 (China)
Market Group:	Endocrine
Lead Company:	Hansoh Pharmaceutical Group Company Limited (3692)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Efficacy and Safety of HS-20094 in Patients with Type 2 Diabetes—A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Trial" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

HS-20094 is a novel dual GIP and GLP-1 receptor agonist. A 4-week POC study was conducted to assess the preliminary efficacy and safety of HS-20094 in patients with type 2 diabetes (T2DM).

Methods

This was a randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov number, NCT06118008). Patients with T2DM poorly controlled with diet and exercise alone or with stable metformin (HbA1c ≥7.0 to ≤10.0%) were randomly (4:1:1) assigned within each cohort to receive HS-20094 (5mg, 10mg or 15mg), semaglutide (1.0mg), or placebo subcutaneously once-weekly. The primary outcome was the change in HbA1c from baseline to week 4. Efficacy results between groups were compared using analysis of covariance (ANCOVA) with baseline value as a covariate and status of metformin use as a fixed effect.

Results

Totally, 54 subjects received at least one dose of HS-20094, semaglutide or placebo. Least square mean (LSM) change in HbA1c was -0.63%, -0.75%, -0.84%, and -0.59% in HS-20094 of 5mg, 10mg, 15mg and semaglutide, respectively (all $p<0.01$ vs placebo). LSM change in fasting blood glucose in corresponding cohort was -2.87, -2.25, -2.79, and -1.92mmol/L, respectively (all $p<0.01$ vs placebo). LSM percent change in body weight was -1.27%, -2.51%, -4.41%, and -1.35%, respectively ($p = 0.192$, $p= 0.016$, $p<0.001$, and $p = 0.179$ vs placebo). The occurrence of adverse events (AEs) was not dose-dependent in HS-20094. The most common AE included decreased appetite, abdominal distension and vomiting. No severe hypoglycemia was reported.

Conclusions

In patients with T2DM, HS-20094 was generally safe and showed meaningful HbA1c, fasting blood glucose and body

weight reductions.

Comment

HS-20094 is a novel long-acting dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes. Topline results from the Phase II trial of HS-20094 in patients with type 2 diabetes poorly controlled with diet and exercise alone or with stable metformin (HbA1c ≥7.0% to ≤10.0%) showed that HS-20094 has a favorable pharmacokinetic profile, with exposure increasing in a dose-dependent manner. Regarding glycemic control, all doses of HS-20094 significantly decreased fasting blood glucose and HbA1c from baseline compared to placebo. HS-20094 doses showed reductions in HbA1c from baseline of -1.06%, -1.24%, and -1.19%, respectively, compared to -1.01% for semaglutide. Notably, HS-20094 showed statistically greater reductions in blood glucose than semaglutide. Body weight was also reduced in a dose-dependent manner in the HS-20094 dose groups, with the highest dose achieving a statistically greater change in body weight from baseline compared to semaglutide. Regarding safety and tolerability, the occurrence of AEs was not dose-dependent for HS-20094, and the most common AEs were decreased appetite, abdominal distension, and vomiting, which are expected side effects of a dual GIP/GLP-1 agonist. Findings show HS-20094 to be generally safe and well tolerated, while displaying meaningful reductions in fasting blood glucose, HbA1c, and body weight that are comparable or superior to semaglutide. However, there are of course limitations to conclusions drawn from the data as this study was relatively short and conducted in a reasonably small sample size (n=54). Despite the limitations, these data support further clinical evaluation and development of HS-20094, suggesting that dual agonism of GLP-1/GIP may offer improved glycemic control and body weight reductions compared to GLP-1 agonism alone.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 733-P)
Citeline Analysis

HTD1801 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - T2DM+NAFLD (China)
Market Group:	Endocrine
Lead Company:	HighTide Therapeutics Inc. (2511)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Berberine Ursodeoxycholate (HTD1801) Improves Key Glycemic and Cardiometabolic Parameters across the Type 2 Diabetes Mellitus Disease Spectrum" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

HTD1801 is a gut-liver anti-inflammatory metabolic modulator shown to improve key glycemic and cardiometabolic parameters. The aim of this study was to evaluate the effectiveness of HTD1801 across the T2DM disease spectrum.

Methods

In a Ph2 study of treatment-naïve patients with T2DM 113 patients were randomized 1:1:1 to placebo (n=38), HTD1801 500 mg BID (n=37), and 1000 mg BID (n=38) for 12 weeks. Key inclusion criteria included T2DM (WHO criteria), HbA1c 7%-10.5% and FPG <13.9 mmol/L. The primary endpoint was change from baseline (BL) in HbA1c at Week 12. For this analysis, patients were assigned to high/low risk groups by BL HbA1c above/below 8.5%.

Results

At BL, 35% of patients had HbA1c ≥8.5%. BL characteristics were balanced between treatment groups and subgroups. Patients with elevated HbA1c had elevated glycemic and cardiometabolic parameters at BL. Treatment with HTD1801 for 12 weeks resulted in a dose dependent reduction across both subgroups (Table). Improvements with 1000 mg BID were significant vs placebo at Week 12. HTD1801 patients with higher HbA1c had more substantial reductions across all parameters compared to patients with lower HbA1c.

Conclusions

Regardless of BL disease severity, HTD1801 treatment resulted in significant improvements in key glycemic and cardiometabolic parameters. HTD1801 continues to be evaluated for T2DM in Ph3 studies.

Comment

Berberine ursodeoxycholate is a gut-liver anti-inflammatory modulator that has been shown to improve glycemic and cardiometabolic parameters. Data from a Phase II study in 113 treatment-naïve patients with type 2 diabetes show berberine ursodeoxycholate treatment for 12 weeks resulted in significant, dose-dependent improvements in glycemic and cardiometabolic parameters, regardless of baseline disease severity, with those with more severe disease (baseline HbA1c ≥8.5%) experiencing the greatest improvements. Interestingly, preclinical research suggests that berberine ursodeoxycholate is associated with positive changes in the components of the gut microbiota, which has been shown to be involved in the pathogenesis of hepatic and metabolic diseases. As such, berberine ursodeoxycholate shows promise as a novel therapeutic with a distinct mechanism of action for the treatment of type 2 diabetes.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 847-P)
Citeline Analysis

HMS5552 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase I - Cross-over Study
Market Group:	Endocrine
Lead Company:	Hua Medicine (Shanghai) Ltd. (2552)
Partner Companies:	Bayer (BAYN) Roche (ROG) Sinopharm Group (1099)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	1% (5% Below Avg.)
Average Approval:	6%

An abstract entitled "Effect of Dorzagliatin, a Dual-Acting Glucokinase Activator, on Insulin and Glucagon Secretion in Impaired and Normal Glucose Tolerance" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Dorzagliatin is a novel dual-acting allosteric activator of hepatic and beta-cell glucokinase (GCK). Dorzagliatin improved second-phase insulin secretion in type 2 diabetes and heterozygous carriers of GCK mutations.

Methods

We investigated the effects of dorzagliatin on insulin secretion and glucagon suppression during hyperglycemic clamps in individuals with impaired glucose tolerance (IGT) and normal controls. In a double-blind, single-dose, randomized cross-over study, 9 participants with IGT (mean age 55±7.5years, 5 female) and 10 controls (39.5±11.8 years, 5 female) underwent 2-hour 12 mmol/l hyperglycemic clamp following a single dose of dorzagliatin 50mg or matched placebo. Insulin, C-peptide and glucagon were measured at regular intervals.

Results

In controls, dorzagliatin significantly increased basal insulin (48.2±26.5 vs 36.8±16.6 pmol/L, p=0.0006) and second-phase insulin area under the curve (AUC) (25164 ± 22525 vs 17533 ± 12043 pmol/L.min, p=0.049) compared with placebo. Glucagon was also significantly suppressed after dorzagliatin (AUC0-120min 161±58 vs 234±70 pmol/L.min, p=0.0009) in the control group. The IGT group showed significantly higher steady-state C-peptide response (2193±531 vs 1768±351 pmol/L, p=0.013) following dorzagliatin, but similar basal, acute insulin secretion and glucagon levels following both treatments. Dorzagliatin did not affect the insulin sensitivity in either subject group.

Conclusions

Dorzagliatin increased second-phase insulin secretion in IGT, while additionally suppressing glucagon and enhancing basal insulin secretion in normal controls.

Comment

Dorzagliatin, an oral dual-acting allosteric activator of hepatic and beta-cell glucokinase, enhances glucokinase activity in a glucose-dependent manner and improves glucose-stimulated insulin secretion. A double-blind, single-dose, randomized crossover Phase I study investigated the effects of dorzagliatin on insulin secretion and glucagon suppression during hyperglycemic clamps in individuals with impaired glucose tolerance (IGT) and normal glucose tolerance controls. Nine participants with IGT and 10 controls underwent hyperglycemic clamp, the gold standard in assessing insulin secretion, following a single dose of dorzagliatin (50mg) or placebo, and levels of insulin, C-peptide, and glucagon were measured at regular intervals. In controls, dorzagliatin significantly increased basal insulin and second-phase insulin AUC compared with placebo. In the IGT group, dorzagliatin showed significantly higher second-phase C-peptide responses compared to placebo, but similar basal, acute insulin secretion, and glucagon levels following both treatments. Enhancing insulin secretion in the second phase is a particularly exciting finding as this is often impaired in type 2 diabetics. Overall, results show that dorzagliatin appears to improve insulin secretion and may be beneficial for glycemic control, deeming further clinical evaluation as warranted.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1887-LB)
Citeline Analysis

HD-6277 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - HT-006-02 (Korea)
Market Group:	Endocrine
Lead Company:	Hyundai Pharm Co., Ltd (A004310)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Efficacy and Safety of HD-6277, a Novel GPR40 Agonist, in Patients with Type 2 Diabetes—A Double-Blind, Randomized, Placebo-Controlled, Parallel-Group, Multicenter Phase 2 Trial" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

To assess the efficacy and safety of HD-6277, the first candidate of GPR40 in a new oral antidiabetic agent, in Adult Patients With Inadequate Control of Type 2 Diabetes Mellitus (T2DM)

Methods

A double-blind, randomized, placebo-controlled phase 2 trial recruited 112 participants aged ≥ 20 years with T2DM with HbA1c between 7.0% and 10.0% while on diet and exercise alone for at least 8 weeks prior to screening. Parallel-group, randomized trial of HD-6277 50mg and 100mg group versus placebo were assigned for 12 weeks. The primary outcome was change in HbA1c at week 12 from baseline. Secondary outcomes included proportion of patients achieving HbA1c less than 7.0%, change in fasting plasma glucose(FPG), Changes in blood levels of post-meal glucose, insulin, glycoalbumin(GA), and C-peptide at week 12. In addition, changes in fasting lipid parameters, weight, GA/HbA1c ratio, HOMA (Homeostasis Model Assessment) β, and CD 36 were evaluated as exploratory endpoints.

Results

At week 12, compared to the placebo group, HD-6277 50mg and 100mg resulted in a statistically significant reduction of HbA1c levels by -0.73(95% CI -1.11, -0.35), p=0.0002 and -0.85 (95% CI -1.21, -0.50), P<0.0001, respectively. No significant increase in treatment-related adverse events was observed for HD-6277. Furthermore, significant improvements in FPG and GA levels were confirmed in the HD-6277 administration group compared to the placebo.

Conclusions

HD-6277 50mg and 100 mg improved glycaemic control in patients with T2DM inadequately controlled with diet and exercise, as shown by significant changes in HbA1c and FPG. The treatment with HD-6277 appeared to be safe and well

tolerated. A GPR40 agonist represents a potential new treatment option for T2DM.

Comment

Activation of G-protein coupled receptors 40 (GRP40) has been shown to lead to increased insulin secretion solely in the presence of elevated glucose levels. HD-6277 is a highly potent, oral, small molecule, selective GPR40 agonist that has been evaluated in a Phase II study in adult patients with inadequate control of type 2 diabetes. Findings show HD-6277 treatment resulted in a statistically significant reduction of HbA1c levels of -0.73% and -0.85%, respectively, compared to placebo at Week 12, as well as improvements in fasting blood glucose. Importantly, the evaluation of safety outcomes revealed no significant increases in treatment-related AEs and liver function tests. Though data show HD-6277 as a promising potential new treatment option, these results are from a relatively small population and further long-term evaluation in clinical trials is warranted.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 853-P)
Citeline Analysis

Awiqli for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - ONWARDS 2 Phase III - ONWARDS 3 Phase III - ONWARDS-4 Phase IIIa - ONWARDS 1 Phase IIIa - ONWARDS-5
Market Group:	Endocrine
Lead Company:	Novo Nordisk A/S (NVO)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	88% (2% Above Avg.)
Average Approval:	86%

An abstract entitled "Efficacy and Safety of Once-Weekly Insulin Icodec vs. Once-Daily Basal Insulin in Individuals with Type 2 Diabetes by Kidney Function—ONWARDS 1–5" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

This post hoc analysis assessed the efficacy and safety of once-weekly insulin icodec (icodec) vs once-daily (OD) basal insulin in insulin-naive (ONWARDS 1, 3, 5) and insulin-experienced (ONWARDS 2, 4) adults with T2D by kidney function subgroup.

Methods

Treatment outcomes were analyzed by kidney function subgroup (eGFR ≥90; eGFR ≥60-<90; eGFR ≥30-<60; eGFR <30; all mL/min/1.73m2).

Results

In ONWARDS 1, 3, and 5, there were no statistically significant treatment by kidney function subgroup interactions for change in A1C from baseline to planned end of treatment (EOT); however, in ONWARDS 2 and 4, there were significant subgroup interactions. No trend for heterogeneity was observed by kidney function subgroup for overall rates of clinically significant or severe hypoglycemia. Across kidney function subgroups, the proportion of participants achieving A1C <7% without clinically significant or severe hypoglycemic episodes at EOT was similar or higher for icodec vs comparators. Additionally, there were no statistically significant differences in average weekly insulin doses for icodec vs OD comparators by kidney function subgroup during the last 2 weeks of treatment in ONWARDS 1-5.

Conclusions

Overall, the efficacy and safety for once-weekly icodec vs OD comparators was consistent, with no trend across kidney function subgroups.

Comment

A number of new post-hoc analyses from the ONWARDS program of insulin icodec in type 2 diabetes were presented, covering both insulin-naïve and insulin-experienced diabetics. Similar or greater reductions in HbA1c and comparable rates of hypoglycemia were observed for insulin icodec compared to daily basal insulin in all trials (except ONWARDS 4) irrespective of insulin experience, age, ethnicity and race, and GLP-1 usage. The ONWARDS 4 trial enrolled insulin-experienced diabetics on a basal/bolus insulin regimen, and ONWARDS 2 enrolled insulin-experienced patients on a basal regimen, whereas the other ONWARDS studies only enrolled insulin-naïve patients. In ONWARDS 4, HbA1c reductions for patients over 65 years of age receiving insulin icodec were inferior to those on a basal/bolus regimen, and it could well be that the complexity of the insulin regimen in these patients is at least in part responsible for these findings. Furthermore, although there were no statistically significant treatment interactions by kidney function subgroup for change in HbA1c in ONWARDS 1, 3, or 5, there were significant subgroup interactions in ONWARDS 2 and 4, primarily driven by patients with mild kidney impairment. To summarize, these findings provide evidence that insulin icodec has the potential to be a valuable and more convenient treatment option for type 2 diabetics, exhibiting excellent glycemic control in patients with varied insulin experience and of differing race, ethnicity, and age, as well as compatibility with existing GLP-1 regimens.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 826-P)
Citeline Analysis

Soliqua 100/33 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data (Clinical Analysis)
Trial Name:	Phase IV – Real-World Studies
Market Group:	Endocrine
Lead Company:	Sanofi (SNY)
Partner Companies:	Alkermes (ALKS) Royalty Pharma (RPRX) Zealand Pharma (ZEAL)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "A Real-World Study Assessing the Efficacy and Safety of Switching from Basal–Bolus Insulin Therapy to Once-Daily iGlarLixi in People with Type 2 Diabetes—Soli De-escalation" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Basal bolus insulin (BBI) therapy is associated with body weight (BW) gain and an increased risk of hypoglycemia, further increasing the treatment burden for people with T2D. This real-world study assessed the efficacy and safety of switching from BBI to iGlarLixi, a once-daily fixed-ratio combination of insulin glargine 100 U/mL plus lixisenatide, in people with T2D.

Methods

This real-world retrospective study included people with T2D (≥18 years) who received ≥1 iGlarLixi prescription during the identification (ID) period following prior treatment with BBI using the Optum Market Clarity® electronic medical record dataset of people with T2D from the United States. The primary endpoint was HbA1c change at 6 months. Secondary endpoints were HbA1c change at 3 months, BW change and hypoglycemic event rate at 6 months.

Results

In total, 11,887 people received ≥1 iGlarLixi prescription during the ID period, and of these, 372 had switched from a BBI regimen to iGlarLixi (mean age, 59 years; mean baseline HbA1c, 9.55%; mean baseline BW, 101.9 kg). From baseline to Month 6, switching to iGlarLixi resulted in a significant mean HbA1c reduction of −0.93% (95% confidence interval [CI]: −1.13, −0.74; p<0.0001) to 8.61% (n=372). At Month 3, HbA1c was 8.68% (n=204). The mean change in BW at 6 months was −0.89 kg (95% CI: −1.61, −0.18; n=359). The hypoglycemia event rate was 46.24 per 100 person-years of follow-up (P100PYFU) at baseline and 40.32 P100PYFU (event rate ratio: 0.77; 95% CI: 0.57, 1.05) after 6 months of iGlarLixi treatment.

Conclusions

In a real-world setting, people with T2D and elevated HbA1c switching from a BBI regimen to a once-daily injection of iGlarLixi achieved lower HbA1c, weight benefit and numerically lower hypoglycemic events.

Comment

A real-world retrospective study assessed the efficacy and safety of switching from basal/bolus insulin to iGlarLixi in type 2 diabetics. Using an electronic medical record dataset of people with type 2 diabetes (aged ≥18 years) from the US who received ≥1 iGlarLixi prescription during the identification period following prior treatment with a basal/bolus regimen, 372 valid participants were identified. In a real-world setting, switching to iGlarLixi led to improved glycemic control, better weight loss, and fewer hypoglycemia events compared to a basal/bolus insulin regimen. Of note, the reduction in treatment burden associated with switching from a basal/bolus insulin regimen to once-daily iGlarLixi may be very desirable to patients with inadequate glycemic control that likely administer multiple daily injections. As such, this study suggests that iGlarLixi is a good option for type 2 diabetes patients struggling to reach their diabetic goals on a basal/bolus insulin regimen.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1867-LB)
Citeline Analysis

Soliqua 100/33 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - LPS17396 (China)
Market Group:	Endocrine
Lead Company:	Sanofi (SNY)
Partner Companies:	Alkermes (ALKS) Royalty Pharma (RPRX) Zealand Pharma (ZEAL)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Efficacy and Safety of iGlarLixi vs. IDegAsp in Chinese People with Type 2 Diabetes (T2D) Suboptimally Controlled with Oral Antidiabetic Drug(s) (OAD)—The SoliD Randomized Controlled Trial" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

SoliD (NCT05413369) compared the efficacy and safety of iGlarLixi, a fixed-ratio combination of insulin glargine 100 U/mL + lixisenatide, vs insulin degludec + insulin aspart (IDegAsp) in Chinese people with T2D suboptimally controlled with OAD(s).

Methods

In this 24-week, multicenter, open-label, Phase 3 study, insulin-naïve people with HbA1c 7-11% were randomized 1:1 to once-daily iGlarLixi (n=291) or IDegAsp (n=291), with continued metformin ± sodium-glucose co-transporter-2 inhibitors. The primary endpoint was noninferiority in HbA1c change from baseline to Week 24. Secondary endpoints included superiority for HbA1c change, body weight (BW) change, proportion of people with HbA1c <7.0% at Week 24, composite endpoints, and hypoglycemia rates.

Results

At Week 24, iGlarLixi demonstrated noninferiority, with least squares (LS) mean difference −0.20 (95% confidence interval [CI]: −0.33, −0.07; p<0.001) and superiority (97.5% CI: −0.35, −0.05; p=0.003) vs IDegAsp in HbA1c reduction. iGlarLixi resulted in a decrease in BW and IDegAsp resulted in an increase in BW from baseline to Week 24, with a LS mean difference of −1.49 kg (97.5% CI: −2.32, −0.66; p<0.001). Other secondary endpoints at Week 24 also favored iGlarLixi vs IDegAsp, respectively (p<0.001 for all): HbA1c <7.0% (72.5% vs 59.8%); HbA1c <7.0% + no BW gain (40.5% vs 21.3%); HbA1c <7.0% + no hypoglycemic events (26.5% vs 13.4%). Event rates (per-person-year) for

American Diabetes Association (ADA) Level 1, 2 or 3 hypoglycemia were lower for iGlarLixi (1.90) vs IDegAsp (2.72) (relative risk: 0.71; 95% CI: 0.52, 0.98). No ADA Level 3 hypoglycemia or unexpected safety findings were reported.

Conclusions

In Chinese people with T2D, suboptimally controlled on OAD(s), iGlarLixi achieved superior improvements in glycemic control, prevention of BW gain and a lower hypoglycemic event rate vs IDegAsp.

Comment

Results from the Phase III SoliD study of iGlarLixi compared to IDegAsp, a once-daily combination of Tresiba and insulin aspart, in Chinese patients with suboptimally controlled type 2 diabetes were presented in a late-breaking abstract. Data showed that iGlarLixi offers better glycemic control, a reduction in body weight instead of an increase, and a lower risk of hypoglycemia compared to IDegAsp. iGlarLixi demonstrated superiority to IDegAsp in HbA1c reductions, as well as eliciting a reduction in body weight, whereas an increase in body weight was observed in patients receiving IDegAsp. The proportion of patients achieving HbA1C <7% was numerically higher for iGlarLixi than IDegAsp (72.5% vs. 59.8%), as was the proportion of patients achieving HbA1C <7% without body weight gain (40.5% vs. 21.3%) and HbA1c <7% without body weight gain plus no hypoglycemic events (26.5% vs. 13.4%). With respect to safety, rates of level 1–3 hypoglycemia were numerically lower for iGlarLixi than IDegAsp (1.90 vs. 2.72 events/person-year). In summary, these results suggest that patients with inadequately controlled diabetes who are currently on basal/bolus insulin regimens such as IDegAsp may be better off switching to a fixed-ratio combination with a GLP-1 agonist such as iGlarLixi. Given that weight loss has become a growing focus in the management of diabetes alongside glycemic control, iGlarLixi may be a useful treatment option for patients to reach their treatment goals.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1869-LB)
Citeline Analysis

GSBR-1290 for Diabetes Mellitus, Type II

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase Ib/IIa - GSBR-1290-02
Market Group:	Endocrine
Lead Company:	Structure Therapeutics, Inc. (GPCR)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	15% (Same As Avg.)
Average Approval:	15%

An abstract entitled "A Phase 1b/2a Study of the Safety and Tolerability of GSBR-1290, a Novel Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA), in Healthy Overweight/Obese Volunteers (HOV) and Participants with Type 2 Diabetes Mellitus (T2DM)" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

GSBR-1290 is a novel, oral, non-peptide GLP-1RA and a potential alternative to injectable or oral peptides used for the treatment of T2DM and obesity. These studies were designed to evaluate the safety, tolerability, and efficacy of GSBR-1290.

Methods

Phase 1b: The safety and tolerability of multiple ascending doses of GSBR-1290 (5-90mg) and its effects on body weight (BW) were investigated in 24 HOV over 4 weeks. Phase 2a: The effects of GSBR-1290 on safety, tolerability, HbA1c, glucose, and BW were investigated in 54 participants with T2DM (45 and 90mg) over 12 weeks and in an interim 8-week analysis of 40 HOV (120mg).

Results

Phase 1b: There were no study discontinuations (d/c) due to adverse events (AEs). Most AEs were mild and GI-related, consistent with GLP-1RAs. BW was significantly reduced (up to 4.9% placebo-adjusted, p=0.013) over 4 weeks. Phase 2a T2DM: Two participants d/c from the study due to an AE (1 attributed to study drug: 2.8% d/c rate). Placebo-adjusted HbA1c (45 mg: -1.01%, p=0.008; 90 mg: -1.02%, p=0.001), BW (45 mg: -3.51%, p=0.0019; 90 mg: -3.26%, p=0.0013), and plasma glucose (45 mg: -2.70, p=0.01; 90 mg: -2.50, p=0.0008) were significantly reduced at day 84. Phase 2a Obesity: There were no study d/c due to AEs. Placebo-adjusted BW decreased though day 56 (120 mg: -4.74%; p<0.0001). Complete 12-week results from the cohort of 24 additional participants will be available at presentation. For all phase 2a, AEs were mild-moderate and GI-related, with no SAEs related to GSBR-1290. Conclusions: GSBR-1290 demonstrated favorable safety and tolerability in this Phase 1b/2a study in participants with T2DM and in HOV. GSBR-1290 demonstrated

clinical benefits in lowering BW, blood glucose, and HbA1c. These data provide clinical proof-of-concept of GSBR-1290 and support further clinical development in T2DM and obesity.

Conclusions

GSBR-1290 demonstrated favorable safety and tolerability in this Phase 1b/2a study in participants with T2DM and in HOV. GSBR-1290 demonstrated clinical benefits in lowering BW, blood glucose, and HbA1c. These data provide clinical proof-of-concept of GSBR-1290 and support further clinical development in T2DM and obesity.

Comment

Results from a Phase Ib/IIa trial of Structure Therapeutics' oral small molecule GLP-1 agonist GSBR-1290 were outlined in a presentation at the conference. The Phase IIa portion evaluated the effects on HbA1c, glucose, and body weight in 54 participants with type 2 diabetes (doses of 45mg and 90mg) over 12 weeks and in an interim eight-week analysis of 40 HOV (120mg dosing). At day 84 in the type 2 diabetes arm, both the 45mg and 90mg doses achieved statistically significant reductions in placebo-adjusted HbA1c (45mg: -1.01%; 90mg: -1.02%), body weight (45mg: -3.51%; 90mg: -3.26%), and plasma glucose (45mg: -2.70; 90mg: -2.50). Only two discontinuations occurred in patients with type 2 diabetes, one of which was attributed to GSBR-1290. These results have further established the safety, tolerability, and efficacy of GSBR-1290 and its potential as an alternative to injectable treatments used for type 2 diabetes. However, this was a relatively small Phase Ib/IIa study, and as such longer-term data from a Phase IIb 36-week obesity study using a tablet formulation are eagerly awaited.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 767-P)
Citeline Analysis

Ozempic for Diabetic Nephropathy

Event Date:	06/24/2024
Event Type:	Trial Data - Final Results (Clinical Analysis)
Trial Name:	Phase III - FLOW
Market Group:	Endocrine
Lead Company:	Novo Nordisk A/S (NVO)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	2%
Likelihood of Approval:	95% (9% Above Avg.)
Average Approval:	86%

	Difference Between Treatment and Placebo
Treatment Description	Semaglutide vs. Placebo
Number of Patients	3533
Number of Evaluable Patients	N/A
Reduction in Kidney Disease Progression and Cardiovascular and Kidney Mortality Risk ***(Endpoint=Primary)***	24 % (P=0.0003)
Reduction in the Mean Annual Glomerular Filtration Rate (eGFR) Slope ***(Endpoint=Secondary)***	1.16 mL/min/1.73m2 (P<0.001)
Risk of Major Cardiovascular Events ***(Endpoint=Secondary)***	N/A (P=0.029)
Risk of Death from any Cause ***(Endpoint=Secondary)***	N/A (P=0.01)

Novo Nordisk presented the full results from FLOW, its Phase IIIb kidney outcomes trial investigating the effects of once-weekly injectable semaglutide 1 mg in adults with type 2 diabetes and chronic kidney disease (CKD) at the Annual Scientific Sessions of the American Diabetes Association (ADA). The article entitled "Effects of semaglutide with and without concomitant SGLT2 inhibitor use in participants with type 2 diabetes and chronic kidney disease in the FLOW trial" was published in *Nature Medicine* on June 24, 2024.

Data from this study were last seen in May 2024.

Context

Novo Nordisk stopped the FLOW study early based on a recommendation from an Independent Data Monitoring Committee due to meeting prespecified efficacy criteria after a median follow-up of 3.4 years.

Based on data from the FLOW clinical trial, Novo Nordisk submitted a label extension application for Ozempic, which has been accepted for review by the U.S. Food & Drug Administration (FDA). A decision is anticipated in January 2025. Data from the FLOW trial were previously presented in May 2024 at the 61st European Renal Association Congress and simultaneously published in the *New England Journal of Medicine*.

Design

FLOW was an international, randomized, double-blind, parallel-group, placebo-controlled, event-driven superiority trial comparing injectable semaglutide 1 mg with placebo as an adjunct to standard of care on kidney outcomes for reducing the risk of progression of kidney impairment and risk of kidney and cardiovascular mortality in people with type 2 diabetes and CKD (defined as eGFR ≥50 and ≤75mL/min/1.73 m^2 and UACR >300 and <5000 mg/g or eGFR ≥25 and <50 mL/min/1.73 m^2 and UACR >100 and <5000 mg/g). 3,533 people (1,767 in the semaglutide group and 1,766 in the placebo group) were enrolled in the trial conducted in 28 countries at around 400 investigator sites. The FLOW trial was initiated in 2019.

Per the abstract, FLOW trial participants with T2D and CKD were stratified by baseline SGLT2i use (N = 550) or no use (N = 2,983) and randomized to semaglutide/placebo.

Endpoints

The key objective of the FLOW trial was to demonstrate delay in the progression of CKD and a lower risk of kidney and cardiovascular mortality through the composite primary endpoint consisting of the following five components: onset of persistent ≥ 50% reduction in eGFR according to the CKD-EPI equation compared with baseline, onset of persistent eGFR (CKD-EPI) < 15 mL/min/1.73 m^2, initiation of chronic kidney replacement therapy (dialysis or kidney transplantation), death from kidney disease or death from cardiovascular disease. Confirmatory secondary endpoints included annual rate of change in eGFR (CKD-EPI), MACE (non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) and all-cause death.

Results

The study achieved its primary endpoint, with semaglutide 1 mg demonstrating a 24% reduction in the risk of kidney disease progression and cardiovascular and kidney mortality compared to placebo (331 vs. 410 events; hazard ratio: 0.76 [0.66; 0.88]; p=0.0003).

The study found that semaglutide 1 mg demonstrated superiority to placebo for all confirmatory secondary outcomes assessed, including a significant reduction in the mean annual glomerular filtration rate (eGFR) slope by 1.16 ml/min/1.73 m²/year (−2.19 vs. −3.36 ml/min/1.73 m²/year [0.86; 1.47]; p<0.001). The risk of major cardiovascular events was significantly lower in the semaglutide group than in the placebo group (212 vs. 254 events; hazard ratio: 0.82; [0.68; 0.98]; p=0.029). The risk of death from any cause was lower in the semaglutide group than in the placebo group (227 vs. 279 events; hazard ratio: 0.80 [0.67; 0.95]; p=0.01).

Per the abstract, the primary outcome occurred in 41/277 (semaglutide) versus 38/273 (placebo) participants on SGLT2i at

baseline (HR 1.07; 95% CI 0.69, 1.67; p=0.755), and in 290/1,490 versus 372/1,493 participants not taking SGLT2i at baseline (HR 0.73; 0.63, 0.85; p<0.001; p-interaction 0.109). Three confirmatory secondary outcomes were predefined. Treatment differences favoring semaglutide for total eGFR slope (ml/min/1.73m^2/year) were 0.75 (–0.01, 1.5) in the SGLT2i subgroup and 1.25 (0.91, 1.58) in non-SGLT2i-subgroup, p-interaction 0.237. Semaglutide benefits on major cardiovascular events and all-cause death were similar regardless of SGLT2i use (p-interaction 0.741 and 0.901, respectively). The benefits of semaglutide in reducing kidney outcomes were consistent in participants with/without baseline SGLT2i use; power was limited to detect smaller but clinically relevant effects.

Most Common Adverse Events

Serious adverse events were reported in fewer participants in the semaglutide group than in the placebo group (877 [49.6%] vs. 950 [53.8%]). Prespecified adverse events of special interest (≥5%) for participants in the semaglutide and placebo groups, respectively, included diabetic retinopathy (402 [22.8%] vs. 398 [22.5%], Covid-19-related disorder (358 [20.3%] vs. 404 [22.9%]), serious cardiovascular disorder (273 [15.4%] vs. 319 [18.1%], heart failure (133 [7.5%] vs. 175 [9.9%]), acute kidney failure (172 [9.7% vs. 182 [10.3%]), malignant tumor (120 [6.8%] vs. 104 [5.9%]) and serious gastrointestinal disorder (95 [5.4%] vs. 94 [5.3%]). Adverse events leading to permanent discontinuation of semaglutide or placebo were more common in the semaglutide group than in the placebo group (233 [13.2%] vs. 211 [11.9%]); this finding was driven mainly by discontinuation because of gastrointestinal disorders (79 [4.5%] vs. 20 [1.1%]).

Conclusion

Semaglutide 1 mg demonstrated a reduction of 24% in the risk of kidney disease-related events vs. placebo in adults with type 2 diabetes and chronic kidney disease.

Comment

This presentation confirms the benefit of semaglutide in patients with type 2 diabetes and chronic kidney disease (CKD), and provides details on the impact of the drug on the progression of renal impairment via eGFR. Moreover, the benefits are consistent whether or not the study participants were receiving an SGLT-2 inhibitor, a class of drug that already has documented renal benefits. With no new safety issues identified and the encouraging topline results confirmed, we are increasing the likelihood of FDA approval of semaglutide for use in CKD patients by another 2%.

Source:

PR Newswire 06/24/2024 (Novo Nordisk)
Journal Article 06/24/2024 (*Nature Medicine*; DOI: 10.1038/s41591-024-03133-0)
American Diabetes Association (ADA)
Citeline Analysis

ZT-003 for Non-Alcoholic Steatohepatitis (NASH)

Event Date:	06/23/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Endocrine
Lead Company:	Beijing QL Biopharmaceutical Co.,Ltd
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	N/A
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

The abstract entitled “A Novel GLP-1/FGF21 Dual Agonist ZT003 Has Therapeutic Potential for Obesity, Diabetes, and Nonalcoholic Steatohepatitis” was presented at the American Diabetes Association (ADA) conference on June 23, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Design

In vitro GLP-1 and FGF21 activities of the fusion protein were measured using a BHK cell line overexpressing human GLP-1 receptor and a HEK293 cell line overexpressing human beta-Klotho. In vivo tests were carried out in DIO mice, db/db mice and NASH mice to demonstrate the pharmacological efficacy of ZT003 on body weight, food intake, plasma glucose, circulating lipids, liver fat content, NAS score and other metabolic parameters as compared to the benchmark molecules. The pharmacokinetic parameters were measured in non-human primates.

Results

ZT003 is an engineered dual agonist fusion protein comprising GLP-1, anti-HSA nanobody (for half-life extension) and FGF21 conjugated with a small molecule to prevent C-terminal degradation. In cell-based assays, ZT003 showed an optimal GLP-1/FGF21 activity ratio. When tested in DIO obese mice and db/db diabetic mice, ZT003 demonstrated synergistic, sustained, and superior body weight reduction and glucose-lowering effect versus semaglutide, tirzepatide and YH25724. When tested in DIO NASH mice, ZT003 significantly improved lipid metabolism, hepatic steatosis, and liver histology, all of these effects being greater than semaglutide. The pharmacokinetic study in cynomolgus monkeys demonstrated the half-life of ZT003 is comparable to that of semaglutide, indicative that ZT003 is likely to be amenable for once-weekly dosing in humans.

Conclusion

In conclusion, this novel GLP-1/FGF21 fusion protein in animals reveals therapeutically efficacious to treat obesity, diabetes, NASH and related co-morbidities, thus demonstrating the promise of the poly-pharmaceutical approach in metabolic drug discovery and development.

Comment

Targeting GLP-1 can lead to appetite suppression and improved glycemic control, whereas targeting FGF21 affects lipid metabolism, suggesting complementary benefits across metabolic diseases, including obesity. Beijing QL Biopharmaceutical's ZT003 is a novel long-acting GLP-1/FGF21 dual agonist in development for type 2 diabetes, obesity, and NASH/MASH.

In obese murine models, ZT003 was superior to semaglutide and tirzepatide for body weight reduction and glucose-lowering effect versus semaglutide, tirzepatide, and YH25724. Weight loss of up to 30% was observed after 28 days of treatment with ZT003. ZT003 returned glucose levels to normal, and insulin sensitivity was also improved. Hamster models for dyslipidemia showed improved TG levels for ZT003 versus semaglutide. In NASH murine models, lipid metabolism, hepatic steatosis, and liver histology were all improved more with ZT003 than with semaglutide.

The half-life of ZT003 was almost the same as that for semaglutide (55.1 hours vs. 55.4 hours), suggesting that this drug candidate could be administered weekly. A Phase II clinical trial is planned for Q2 2025, although the target population was not specified.

Source:

American Diabetes Association (ADA) 06/23/2024 (Abstract 297-OR)
Citeline Analysis

ZP8396 for Obesity

Event Date:	06/24/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Zealand Pharma A/S (ZEAL)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

The abstracts entitled “Petrelintide (ZP8396) Significantly Reduces Fat Mass while Preserving Lean Mass in DIO Rats” and "Petrelintide (ZP8396) Significantly Reduces Fat Mass while Preserving Lean Mass in DIO Rats" were presented at the American Diabetes Association (ADA) conference on June 24, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Context

Petrelintide is currently being explored in a multiple ascending dose (MAD) study to assess the potential for the management of obesity.

Design

Researchers investigated the effect of petrelintide, a novel once-weekly amylin analog on weight loss with comparison of changes of fat mass and lean mass in DIO (diet-induced obese) rats. DIO rats were treated with either vehicle (every second day), liraglutide (5 nmol/kg twice daily) or petrelintide (2 nmol/kg every second day or 10 nmol/kg every fourth day) for a 30-day treatment period. Body weight was measured daily, and body composition was measured by use of EchoMRI at baseline and at day 29 of treatment.

Results

Treatment with liraglutide and petrelintide resulted in significantly lower relative body weight compared to vehicle (3.3 % ± 0.7 vehicle, -0.1 % ± 1.1 liraglutide, -4.1 % ± 0.6 petrelintide 2 nmol/kg, -7.8 % ± 0.7 petrelintide 10 nmol/kg; relative to initial body weights ± SEM). Treatment with petrelintide resulted in significant reduction of fat mass in comparison to vehicle, which liraglutide did not (2.0% ± 0.5 liraglutide, -0.3 % ± 0.5 petrelintide 2 nmol/kg, -1.6 % ± 0.5 petrelintide 10 nmol/kg, 3.2 % ± 0.4 vehicle; mean change in fat mass as % of body weight ± SEM).
Furthermore, treatment with petrelintide resulted in significant preservation of relative lean mass in comparison to vehicle, which liraglutide did not (-3.8 % ± 0.3 vehicle, -2.4 % ± 0.6 liraglutide, -0.8 % ± 0.4 petrelintide 2 nmol/kg, 0.1 % ± 0.4

petrelintide 10 nmol/kg; mean change in lean mass as % of body weight ± SEM).

Conclusion

In conclusion, petrelintide shows preferential fat mass loss and preservation of relative lean mass during weight loss in DIO rats. Based on these findings, petrelintide could hold the potential to reduce the loss of lean body mass associated with weight loss in humans.

Comment

Petrelintide (ZP8396) is an amylin analog designed for once-weekly subcutaneous administration in development by Zealand Pharma. Amylin is a hormone released with insulin from pancreatic beta cells after food is ingested. Activating the amylin receptor is associated with increased satiety and increased leptin sensitivity. These preclinical data support the move of petrelintide into human trials as a weight loss agent that may preserve lean mass.

Source:

American Diabetes Association (ADA) 06/24/2024 (Abstract 1661-P)
American Diabetes Association (ADA) 06/24/2024 (Abstract 1662-P)
Citeline Analysis

ZP8396 for Obesity

Event Date:	06/24/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase Ia - SAD (Healthy Volunteers) Phase Ib - MAD (Healthy Volunteers)
Market Group:	Metabolic
Lead Company:	Zealand Pharma A/S (ZEAL)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

The abstract entitled “Novel Once-Weekly Amylin Analog Petrelintide (ZP8396) Is Well Tolerated with Improved GI Tolerability after Multiple Dosing” was presented at the American Diabetes Association (ADA) conference on June 24, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Data from the Phase Ia SAD study was last seen in June 2023 and data from the Phase Ia MAD study were last seen in June 2024.

Context

Higher doses are being explored to assess the potential for the management of obesity.

Design

56 participants (mean BMI 25.6 kg/m2) were randomized to a SD of petrelintide or placebo (6:2) across seven dose cohorts (0.04 to 2.4 mg). 20 participants (mean BMI 25.4 kg/m2) were randomized to six once-weekly doses (MD) of petrelintide or placebo (7:3) across two dose cohorts (0.6 and 1.2 mg), without dose titration. Body weight reduction and adverse events (AEs) from Gastrointestinal (GI) and Metabolism and Nutrition SOC are compared descriptively.

Results

SD of 1.4 and 2.4 mg resulted in similar exposures in terms of Cmax and AUCtau as MD doses of 0.6 and 1.2 mg at steady state, respectively. The mean body weight reduction was 3.6% and 4.2% in SAD cohorts and 5.3% and 5.1% in MAD cohorts, after one or six weeks of dosing, respectively.

Most Common Adverse Events

All AEs were mild to moderate, with no serious or severe AEs reported, and no treatment discontinuations. No moderate GI AEs were seen after MD. The most frequently related AEs were decreased appetite, nausea and vomiting. A lower

percentage of participants reported nausea or vomiting after MD compared to a SD. For 0.6 mg MD, 14% reported nausea vs 67% for 1.4 mg SD. For 1.2 mg MD, 29% reported nausea vs 83% for 2.4 mg SD. Reporting of vomiting was similarly low for 0.6 mg MD and 1.4 mg SD cohorts, 1 participant in each cohort. For 1.2 mg MD, none reported vomiting whilst 67% reported after 2.4 mg SD. The percentage of participants reporting either decreased appetite and/or early satiety were similar after SD and MD

Conclusion

Results indicate improved GI tolerability of petrelintide when exposure is gradually increased. AEs of decreased appetite and early satiety were similar after SD and MD.

Comment

Petrelintide (ZP8396) is an amylin analog designed for once-weekly subcutaneous administration in development by Zealand Pharma. Amylin is a hormone released with insulin from pancreatic beta cells after food is ingested. Activating the amylin receptor is associated with increased satiety and increased leptin sensitivity. Preclinical data have demonstrated that petrelintide reducse food intake and fat mass supporting the move of petrelintide into human trials.

These Phase I data were from assessments of doses of up to 2.4mg of petrelintide without titration weekly for six weeks in healthy, lean, and overweight males. Results showed that AEs were only mild to moderate, with decreased appetite, nausea, and vomiting being the most commonly reported, although no data on discontinuation rates were reported. Mean body weight reductions of more than 5% were observed over the six-week dosing period. Overall, these data suggest that petrelintide has potential as a weight loss agent and further investigations are warranted.

Source:

American Diabetes Association (ADA) 06/24/2024 (Abstract 1668-P)
Citeline Analysis

Pemvidutide for Obesity

Event Date:	06/23/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - MOMENTUM
Market Group:	Metabolic
Lead Company:	Altimmune Inc. (ALT)
Partner Companies:	N/A
Former Companies:	Spitfire Pharma Inc. Velocity Pharmaceutical Development
Change to Likelihood of Approval:	7%
Likelihood of Approval:	33% (8% Above Avg.)
Average Approval:	25%

Altimmune presented data from the 48-week Phase II MOMENTUM study of pemvidutide for obesity, including the results of a recently completed body composition analysis, at the American Diabetes Association's (ADA) 84th Scientific Sessions. The abstract entitled "Pemvidutide, a GLP-1/Glucagon Dual Receptor Agonist, in Subjects with Overweight or Obesity—A 48-Week, Placebo-Controlled, Phase 2 (MOMENTUM) Trial" was presented at the meeting on June 23, 2024.

Data from this study were last seen in November 2023.

Design

The trial enrolled 391 subjects with obesity, or overweight with at least one co-morbidity and without diabetes. Subjects were randomized 1:1:1:1 to 1.2 mg, 1.8 mg, 2.4 mg pemvidutide or placebo administered weekly for 48 weeks in conjunction with diet and exercise. A subgroup of subjects was evaluated in a body composition analysis.

Per the abstract, MOMENTUM was a Phase II, randomized, placebo-controlled trial of subjects with overweight (BMI 27.0-29.9 kg/m2) and at least one obesity-related comorbidity or obesity (BMI >30.0 kg/m2) randomized 1:1:1:1 to pemvidutide (1.2, 1.8, 2.4 mg) or placebo administered subcutaneously weekly for 48 weeks.

Results

At Week 48, subjects receiving pemvidutide achieved mean weight losses of 10.3%, 11.2%, 15.6% and 2.2% at the 1.2 mg, 1.8 mg, and 2.4 mg doses and placebo, respectively, with a near-linear continued weight loss observed on the 2.4 mg dose at the end of treatment. The full MRI-based body composition analysis included 50 subjects who received pemvidutide and showed that subjects in the pemvidutide groups had an average lean mass loss of 21.9% with 78.1% of weight loss attributable to fat. In addition, pemvidutide resulted in reductions in serum lipids and improvements in blood pressure without imbalances in cardiac events, arrhythmias or clinically meaningful increases in heart rate.

Per the abstract, all doses with 51.8% and 32.1% of subjects at the 2.4 mg dose level achieving ≥15% and ≥20% weight loss and 48% of subjects having resolution of baseline obesity by trial conclusion. Subjects with elevated serum lipids at

baseline had reductions of up to 55.8%, 20.0%, and 21.8% in triglycerides, total cholesterol and LDL at week 48.

Most Common Adverse Events

Per the abstract, most adverse events were mild to moderate with only 1 drug-related SAE; glycemic control (glucose, HbA1c) was maintained with minimal increases in heart rate.

Conclusion

Full analysis of body composition data showed lean mass preservation with 21.9% of weight loss attributable to lean mass and 78.1% attributable to fat.

Comment

Altimmune's pemvidutide is a GLP-1 and glucagon receptor dual agonist in development for obesity and nonalcoholic steatohepatitis (NASH); targeting glucagon aims to provide increased metabolism of lipids including hepatic fat. Pemvidutide has been designed to provide a longer half-life and delayed time to peak concentration that could avoid the need for longer titration periods to reach optimal doses.

In this trial, almost 400 non-diabetic patients with obesity or overweight received pemvidutide 1.2mg, 1.8mg, or 2.4 mg or placebo; only the highest dose of pemvidutide had a four-week titration period. Weight loss of up to 15.6% was achieved with pemvidutide after 48 weeks, with the trends suggesting further reductions are to be expected from longer durations of treatment. Waterfall graphs showed almost all recipients of the top dose achieved some degree of weight loss, with high responders reaching weight loss of more than 30%. Importantly, MRI studies showed that the loss of lean mass accounted for a mean of only 21.9% of the overall weight loss. Cardiometabolic benefits were also demonstrated, including an impressive reduction of more than 50% in triglycerides associated with the top dose of pemvidutide.

Although discontinuation rates for treatment-related AEs approached 20% for the higher doses of pemvidutide, overall discontinuation rates were lower for the active treatment than with placebo (although patients leaving due to the belief they were not receiving active treatment is a driver here). As expected, GI AEs were the most common and were largely mild to moderate in severity; vomiting at the higher doses was experienced by almost 30% of patients. There was no difference in rates of cardiac AEs across the pemvidutide and placebo groups.

These data suggest that not only is pemvidutide a potentially efficacious new therapeutic option for obesity, but it could offer a more convenient option due to the need for no or only limited dose titration when commencing this drug. A concern over the rate of vomiting was noted, but the presenter, Professor Louis Aronne, noted that it was not considered serious, though further refinement of dose titration may be required. Should pemvidutide be able to replicate its impressive efficacy in Phase III trials and also confirm the need for short or no titration, it may be able to gain an advantage over currently marketed competitors. Based on these data we are increasing the likelihood of FDA approval for obesity by 7%.

Source:

Globe Newswire 06/23/2024 (ALT)
PR Newswire 06/23/2024 (American Diabetes Association)
American Diabetes Association (ADA) 06/23/2024 (Abstract 262-OR)
American Diabetes Association (ADA) 06/23/2024 (Presentation Slides)
Citeline Analysis

ZT-003 for Obesity

Event Date:	06/23/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Beijing QL Biopharmaceutical Co.,Ltd
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	N/A
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

The abstract entitled “A Novel GLP-1/FGF21 Dual Agonist ZT003 Has Therapeutic Potential for Obesity, Diabetes, and Nonalcoholic Steatohepatitis” was presented at the American Diabetes Association (ADA) conference on June 23, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Design

In vitro glucagon-like peptide 1 (GLP-1) and fibroblast growth factor 21 (FGF21) activities of the fusion protein were measured using a BHK cell line overexpressing human GLP-1 receptor and a HEK293 cell line overexpressing human beta-Klotho. In vivo tests were carried out in diet induced obese (DIO) mice, db/db mice and NASH mice to demonstrate the pharmacological efficacy of ZT003 on body weight, food intake, plasma glucose, circulating lipids, liver fat content, NAS score and other metabolic parameters as compared to the benchmark molecules. The pharmacokinetic parameters were measured in non-human primates.

Results

ZT003 is an engineered dual agonist fusion protein comprising GLP-1, anti-HSA nanobody (for half-life extension) and FGF21 conjugated with a small molecule to prevent C-terminal degradation. In cell-based assays, ZT003 showed an optimal GLP-1/FGF21 activity ratio. When tested in DIO obese mice and db/db diabetic mice, ZT003 demonstrated synergistic, sustained, and superior body weight reduction and glucose-lowering effect versus semaglutide, tirzepatide and YH25724. When tested in DIO NASH mice, ZT003 significantly improved lipid metabolism, hepatic steatosis, and liver histology, all of these effects being greater than semaglutide. The pharmacokinetic study in cynomolgus monkeys demonstrated the half-life of ZT003 is comparable to that of semaglutide, indicative that ZT003 is likely to be amenable for once-weekly dosing in humans.

Conclusion

In conclusion, this novel GLP-1/FGF21 fusion protein in animals reveals therapeutically efficacious to treat obesity, diabetes, NASH and related co-morbidities, thus demonstrating the promise of the poly-pharmaceutical approach in

metabolic drug discovery and development.

Comment

Targeting GLP-1 can lead to appetite suppression and improved glycemic control, whereas targeting FGF21 affects lipid metabolism, suggesting complementary benefits across metabolic diseases, including obesity. Beijing QL Biopharmaceutical's ZT003 is a novel long-acting GLP-1/FGF21 dual agonist in development for type 2 diabetes, obesity, and NASH/MASH.

In obese murine models, ZT003 was superior to semaglutide and tirzepatide for body weight reduction and glucose-lowering effect versus semaglutide, tirzepatide, and YH25724. Weight loss of up to 30% was observed after 28 days of treatment with ZT003. ZT003 returned glucose levels to normal, and insulin sensitivity was also improved. Hamster models for dyslipidemia showed improved TG levels for ZT003 versus semaglutide. In NASH murine models, lipid metabolism, hepatic steatosis, and liver histology were all improved more with ZT003 than with semaglutide.

The half-life of ZT003 was almost the same as that for semaglutide (55.1 hours vs. 55.4 hours), suggesting that this drug candidate could be administered weekly. A Phase II clinical trial is planned for Q2 2025although the target population was not specified..

Source:

American Diabetes Association (ADA) 06/23/2024 (Abstract 297-OR)
Citeline Analysis

Rejuva for Obesity

Event Date:	06/23/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Fractyl Health (GUTS)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

Fractyl Health announced new data from its preclinical Rejuva pancreatic gene therapy program was presented in an oral presentation entitled "Single-Dose GLP-1-Based Pancreatic Gene Therapy Durably Maintains Body Composition and Glycemia After Semaglutide Withdrawal in a Murine Model of Obesity" at the 84 th American Diabetes Association (ADA) on June 23, 2024.

Design

In the study presented at ADA, obese (DIO) mice were randomized 1:1:1 to one of the following and followed for 4 weeks:

- Arm 1: single administration of a Rejuva GLP-1-based gene therapy candidate,
- Arm 2: daily semaglutide injections, or
- Arm 3: placebo

At the end of 4 weeks, semaglutide was discontinued for mice in Arm 2 and those animals were further randomized 1:1 to receive either a single administration of the Rejuva gene therapy candidate or placebo, and all animals were followed for an additional 4 weeks, leading to the following assessment arms at 8 weeks:

- Arm 1: continued follow-up of a single administration of a Rejuva GLP-1-based gene therapy candidate
- Arm 2a: semaglutide withdrawal at week 4
- Arm 2b: semaglutide withdrawal with crossover to single administration Rejuva at week 4
- Arm 3: continued follow up of placebo

At the end of 8 weeks, the pancreatic islets were then isolated to study the effect of glucose exposure on GLP-1-based transgene release from genetically modified islets.

Results

At week 4, the Rejuva arm experienced reduced fat mass of 21% versus 16% of body weight with semaglutide (both $p<0.0001$ versus placebo, $p<0.05$ Rejuva versus semaglutide) while both Rejuva and semaglutide preserved lean mass with a loss of only 5% of body weight (both, $p<0.0001$ versus placebo).

At week 8, fat mass rebounded to 1% below baseline (n.s.) in the semaglutide withdrawal group (Arm 2a), whereas semaglutide-withdrawn mice treated with Rejuva (Arm 2b) maintained fat reduction of 17% ($p<0.01$) and weight loss of 22% ($p<0.0001$) at week 8.

Glucose and insulin levels in all intervention groups corresponded to changes observed in fat mass, with statistically significant improvements in fasting glucose and fasting insulin in semaglutide-treated and Rejuva treated mice at 4 and 8 weeks, but no improvement in glucose or insulin in semaglutide-withdrawn mice that did not crossover to Rejuva at week 8.

Conclusion

Single administration of Rejuva reduced fat mass and improved glycemia in the well-validated diet-induced obesity (DIO) mouse model. Rejuva also prevented weight and glycemic rebound after semaglutide withdrawal and data provide first demonstration that Rejuva treatment mimics the natural release of GLP-1 from the pancreas.

Comment

Despite the weight loss benefits from GLP-1 receptor agonists, there is increasing evidence that the impact may not be long term, with rebound weight gain a problem if treatment is discontinued. Gene therapies that can alter the expression of key proteins and hormones offer the potential for long-lasting therapeutic interventions with minimal treatment burden. Fractyl Health has developed a novel adeno-associated virus (AAV)-based, pancreatic gene therapy platform designed to provide durable production of GLP-1-based peptides. The therapy is delivered to the pancreas via endoscopy, with this local administration allowing low viral genome dosing and limiting systemic virus exposure.

In the ADA Presidents' Select Abstract, data were presented from a diabetes murine model that evaluated a single-dose intraperitoneal pancreatic gene therapy versus daily subcutaneous semaglutide over 62 days (with corresponding vehicle controls). Significant improvements in fasting blood glucose and fasting plasma insulin were observed for the gene therapy over semaglutide. Significantly greater weight loss was also reported, which can be challenging to demonstrate in the murine model under study. The pancreatic gene therapy was associated with reduced fat mass of 21% and lean mass of 5%, compared with a 16% loss in fat mass and 5% loss of lean mass for semaglutide (all differences, $p<0.0001$). Another trial was conducted in a standard obesity murine model, in which daily semaglutide was administered for 28 days versus a single administration of the pancreatic gene therapy. Following the semaglutide withdrawal, those mice were then randomized to a half-dose of the gene therapy or vehicle controls and followed for another month. Body weight was reduced by approximately 20% with semaglutide after 28 days and by around 25% with the gene therapy at the same time point. Following withdrawal of semaglutide, fat and lean mass increased to 1% and 2% below baseline, but the mice treated with pancreatic gene therapy maintained reductions of 17% ($p<0.01$) and 5% ($p<0.001$), respectively, at Week 8. In the gene therapy and semaglutide groups, fasting glucose was reduced by 18% at Week 4 (both $p<0.0001$). Semaglutide withdrawal resulted in fasting glucose rebound to baseline, while the gene therapy recipients and the half-dose gene therapy-treated mice maintained 21% ($p<0.0001$) and 22% ($p<0.001$) fasting glucose reductions after 8 weeks.

Following the trial, the mice were sacrificed and pancreatic islets were grown in tissue culture and a glucose concentration-dependent assessment of the effect of GLP1 transgene in the tissue media was completed, showing little release under low glucose conditions but high release under high glucose conditions. The amount of total GLP-1 secreted was only a few percent, suggesting the gene therapy offers regulation of GLP-1 with secretory reserve as would be seen in a healthy beta cell. Similar patterns were seen for insulin parameters. No evidence of pancreatic injury or inflammation was identified in any of the groups.

Discussion included the potential for redosing, with the presenter, Dr. Harith Rajagopalan, replying that they believe

the treatment is “one and done” at this stage. Other questions focused on the reversibility of the gene therapy and also on the potential for a positive feedback loop with GLP-1 and insulin signaling. Regarding reversibility, Dr. Rajagopalan noted there were ways to reduce the risk of complications and that there was no evidence of a feedback loop thus far. Fractyl Health’s pancreatic gene therapy has demonstrated nutrient-responsive GLP-1 secretion in pancreatic islets and appears to provide a sustained therapeutic effect following a single administration, giving it the potential to be a ground-breaking novel therapeutic option in type 2 diabetes and obesity.

Source:

Globe Newswire 06/23/2024 (GUTS)
American Diabetes Association (ADA) 06/23/2024 (Abstract 261-OR)
Citeline Analysis

BMS-986089 for Obesity

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Biohaven Ltd. (BHVN)
Partner Companies:	Bristol Myers Squibb (BMY) Roche (ROG)
Former Companies:	Biohaven
Change to Likelihood of Approval:	0%
Likelihood of Approval:	15% (Same As Avg.)
Average Approval:	15%

The abstract entitled “Taldefgrobep Alfa Improves Body Composition as Monotherapy and in Combination with Semaglutide in a DIO Mouse Model” was presented at the American Diabetes Association (ADA) conference on June 22, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Design

Six-week-old C57BL/6J male mice received a HFD for 13 weeks prior to their subcutaneous treatment assignment: vehicle BIW, taldefgrobep 100 mg/kg BIW, semaglutide 20 µg/kg QD, semaglutide 40 µg/kg QD, taldefgrobep 100 mg/kg BIW with semaglutide 20 µg/kg QD or 40 µg/kg QD for 8 weeks. All animals were followed for 4 weeks post-dosing. Body composition (EchoMRI) and metabolic markers were assessed at baseline, posttreatment and study end. Histopathology of adipose, muscle, and liver was also performed.

Results

Within 4 weeks of treatment, all taldefgrobep treatment groups, including monotherapy and combination with semaglutide, demonstrated significant reductions in fat mass and increased lean mass, relative to vehicle or semaglutide alone. The following body composition changes (% fat mass, % lean mass) were observed at 4 weeks: taldefgrobep (-25.8%, +14.9%), vehicle (+6.9%, +6.7%), semaglutide 40 (-11.5%, +0.2%), taldefgrobep/semaglutide 40 (-31.8%, +12.3%). In addition, taldefgrobep-treated mice achieved a significant reduction in TBW relative to vehicle (-6.7%).

Conclusion

This study supports the development of taldefgrobep as a monotherapy or combination with GLP-1R agonists to reduce fat and maintain lean mass in individuals living with overweight and obesity.

Comment

Biohaven's taldefgrobep alfa (BMS-986089) is an investigational fusion protein designed to target myostatin, an endogenous protein that restricts skeletal muscle growth. By blocking activation of myostatin, activin receptor signaling is prevented, leading to muscle hypertrophy and increasing lean muscle mass, alongside benefits in terms of reduced fat mass and increased insulin sensitivity. In a high-fat diet murine model, taldefgrobep alfa monotherapy and in combination with semaglutide was assessed over 12 weeks (including four weeks of follow-up). After four weeks of treatment, taldefgrobep alfa monotherapy was associated with a 25.8% reduction in fat mass and a 14.9% gain in lean mass, vehicle with a 6.9% gain in fat mass and a 6.7% gain in lean mass, semaglutide with an 11.5% reduction in fat mass and a 0.2% gain in lean mass, and the combination of taldefgrobep alfa plus semaglutide was associated with a 31.8% loss of fat mass and a 12.3% gain in lean mass. As many patients lose lean mass during weight loss treatment, taldefgrobep alfa could be incorporated into therapeutic drug regimnes to optimize body composition. Further investigation is warranted.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 2053-LB)
Citeline Analysis

DA-1726 for Obesity

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	NeuroBo Pharmaceuticals, Inc. (NRBO)
Partner Companies:	Dong-A (000640:KS) ImmunoForge
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	15% (Same As Avg.)
Average Approval:	15%

NeuroBo announced that preclinical data of DA-1726 was presented in a poster entitled “DA-1726, a GLP1R/GCGR Dual Agonist, A Promising Approach in Obesity Treatment and Lipid Management” at the American Diabetes Association (ADA) 84th Scientific Sessions on June 22, 2024.

Context

DA-1726 is in Phase I clinical trial. In a prior study, DA-1726 showed a difference in improving lipid levels, despite similar weight loss to tirzepatide.

Design

The direct lipid-regulating effect of DA-1726 was assessed in a hypercholesterolemia rat model compared with tirzepatide.

Results

This study focuses on the pharmacological effects of this oxyntomodulin analogue, which has been effective at improving lipid profiles and reducing weight in rodent models. In an obese mouse model, DA-1726 showed weight loss compared to survodutide (-24.7%, -18.2%; p<0.05 vs. control) while demonstrating body fat mass reduction and relative lean body mass preservation versus survodutide (body fat change -31.4%, -15.1% vs. -8.7% control). DA-1726 also lowered T-CHO (-67.7%, -49.6%; p<0.05 vs. control) and TG (-49.5%, -41.2%; p<0.05 vs. control) while showing glucose lowering compared to survodutide (-54.7%, -30.4% vs. control; p<0.05). Despite the same mechanism of action, DA-1726-treated mice showed weight loss, fat mass reduction and glucose lowering efficacy. This effect might stem from DA-1726's GLP-1 and glucagon receptor activity ratio. DA-1726 have increased the expression of EE-related genes in brown adipose tissue. As a result, DA-1726 was more effective than tirzepatide in suppressing the elevation of T-CHO (-33.5%, -25.5% vs. control; p<0.05) and LDL-C (-53.2%, -41.5% vs. control; p<0.05) despite the two groups of rats consuming the same amount of food. This differentiated impact is thought to arise from DA-1726's glucagon action, alongside its GLP-1 effect. The study evaluated whether these differential effects could also be distinguished from drugs of the same class.

Per the abstract, DA-1726 resulted in similar weight loss effects (-31.9%, -25.4%; P<0.05 vs. control) as survodutide.

Conclusion

The results demonstrated that DA-1726 has differentiating characteristics in the competition of obesity treatment drugs with similar mechanisms in its effect on improving cholesterol metabolism through glucagon action.

Comment

DA-1726 is an oxyntomodulin analog targeting glucagon and GLP-1 receptors in development for obesity with NeuroBo Pharmaceuticals. Targeting GLP-1 and glucagon receptors is associated with suppression of appetite and less food intake, with additional lipid benefits driven by glucagon receptor activity. Preclinical data for DA-1726 have already demonstrated benefits in terms of lipid levels versus tirzepatide despite similar weight loss.

In this presentation, data from a hypercholesterolemia rat model compared DA-1726 with tirzepatide and showed greater reductions in total cholesterol and LDL-C elevations with DA-1726. Further studies using an obese mouse model showed that DA-1726 achieved significantly greater reductions in total cholesterol and triglyceride levels than survodutide, although weight loss was similar. In addition, DA-1726 was more effective for glucose lowering than survodutide. Notably, despite both DA-1726 and survodutide having the same targets, DA-1726-treated mice maintained similar weight loss versus survodutide-treated mice while taking in more food, which was reported to be potentially due to DA-1726's GLP-1 and glucagon receptor activity ratio.

Overall, DA-1726 has the potential to differentiate itself from the competition based on additional lipid profile improvements and weight loss relative to energy intake.

Source:

PR Newswire 06/22/2024 (NRBO)
American Diabetes Association (ADA) 06/22/2024 (Abstract 2058-LB)
American Diabetes Association (ADA) 06/22/2024 (Poster 2058-LB)
American Diabetes Association (ADA) 06/22/2024 (Slides)
Citeline Analysis

PG-102 for Obesity

Event Date:	06/22/2024
Event Type:	Trial Data - Top-Line Results (Clinical Analysis)
Trial Name:	Phase I - SL-MG12-P1
Market Group:	Metabolic
Lead Company:	ProGen Co. Ltd
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

The abstract entitled “PG-102, a Novel Bispecific GLP-1R/GLP-2R Fc-Fused Agonist—Data on Safety, Tolerability, and Pharmacokinetics (PK) in Single Ascending Dose Trial in Healthy Subjects and Preliminary Population PK Modeling” was presented at the American Diabetes Association (ADA) conference on June 22, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Context

These findings will be further refined and updated with the results from the ongoing multiple ascending dose study.

Design

In this Phase Ia study, researchers conducted a randomized placebo-controlled, and double-blind study to evaluate the safety, tolerability, pharmacokinetics (PK), and preliminary pharmacodynamics (PD) of single ascending doses of PG-102 in healthy subjects. Additionally, researchers employed PK/PD modeling to propose preliminary dosing intervals for further clinical studies. Forty volunteers (33 men, 7 women; mean age 30.1 years, mean BMI 23.8 kg/m ^{2}) received PG-102 (5, 15, 30, and 60 mg) or placebo in an 8:2 ratio.

Results

The PK profile demonstrated a prolonged sustenance effect of PG-102, enabling sustained high concentrations in the bloodstream, thereby contributing to its prolonged effectiveness compared to other Fc-fused protein agonist. Utilizing basic population PK modeling with simulated human PK profiles, the researchers proposed efficacious doses and dosing intervals for PG-102. PK/PD modeling suggests weekly injections of 5 mg and 15 mg, and biweekly or longer interval for 30 mg and 60 mg doses. Additionally, simulated dose of 90 mg are expected to have monthly intervals.

Most Common Adverse Events

PG-102 demonstrated acceptable safety and a favorable PK profile. Treatment-emergent adverse events (TEAEs) were primarily gastrointestinal, including dyspepsia, nausea, and vomiting, consistent with the GLP-1RA drug class. Notably, no nausea or vomiting occurred up to the 30 mg dose and TEAEs were generally mild to moderate in severity.

Comment

Although the benefits for obesity and type 2 diabetes from activation of the GLP-1 receptors are well documented, the role of the GLP-2 receptor is still being investigated, with effects on inflammation and satiety having been shown. Based on impressive efficacy data in preclinical studies, doses of up to 60mg of PG-102 were compared with placebo in this Phase I trial. The AE profile was consistent with the known issues with GLP-1 receptor activation, being predominantly GI-related, although no nausea or vomiting occurred up to the 30mg dose. The effect of PG-102 was sustained in the pharmacokinetics studies, suggesting dosing of up to monthly may be possible. These early findings suggest PG-102 may be able to offer additional benefits by targeting the GLP-2 receptor, leading to further reductions in CV risk, and as such data from further clinical trials is keenly awaited.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 1859-LB)
Citeline Analysis

NA-931 for Obesity

Event Date:	06/22/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Biomed Industries, Inc.
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	58% (Same As Avg.)
Average Approval:	58%

The abstract entitled “NA-931, a Novel Triple IGF-1/GLP-1/GIP Incretin Receptor Agonist Reduces Body Weight and Improves Metabolic Profile in DIO Mice” was presented at the American Diabetes Association (ADA) conference on June 22, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Design

Male diet-induced obese (DIO) mice were treated with daily subcutaneous injections of vehicle or one of novel triple IGF-1/GLP-1/GIP receptor agonists, NA-931, NA-932 and NA-933 (10 nmol/kg), for 14 days. Tirzepatide (10 nmol/ kg) as used as positive controls. Cohorts were then assessed for changes in BW, glucose, and lipids.

Results

Treatment with NA-931 Compounds resulted in reductions to BW (up to 26%, $p<0.0001$), plasma glucose, plasma triglycerides, (up to 23% and 34%, respectively, $p<0.003$ for each), and liver triglycerides (up to 46%, $p<0.05$) compared to vehicle treatment. Weight loss effects in cohorts treated with NA-931 Compounds were comparable to those observed in tirzepatide-treated animals. In addition, liver lipid reductions were numerically greater among animals treated with the NA-931Compounds.

Conclusion

NA-931 and its analogs produced significant reductions in BW in DIO mice. Effect sizes were comparable to those observed in the tirzepatide control group. The NA-931 Compounds have been shown to produce desirable changes to lipid profile, suggesting global cardiometabolic benefit, represent a promising therapeutic approach to metabolic disorders such as obesity, type 2 diabetes, and non-alcoholic steatohepatitis.

Comment

Targeting GIP and GLP-1 has been shown to be effective for weight loss in patients with obesity, with Eli Lilly's tirzepatide already having gained approval. Biomed Industries' NA-931 is directed against these receptors but also against insulin-like growth factor 1 (IGF-1), which affects fuel metabolism and regulation of body composition.

In obese murine models, daily subcutaneous injections of three NA-931 analogs administered over 14 days were compared with vehicle and tirzepatide as an active control. Significant body weight reductions of up to 26% were observed with the NA-931 analogs, as well as improvements in plasma glucose and triglyceride levels versus vehicle; hepatic fat was also markedly reduced. Weight loss effects across the NA931 analog cohorts were similar to tirzepatide. These findings support further development of NA-931 for type 2 diabetes, obesity, and NASH.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 2059-LB)
Citeline Analysis

GZR18 for Obesity

Event Date:	06/22/2024
Event Type:	Trial Data - Top-Line Results (Clinical Analysis)
Trial Name:	Phase Ib/IIa - Adult Patients in Obese/Overweight (China)
Market Group:	Metabolic
Lead Company:	Gan & Lee Pharmaceuticals
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

Gan & Lee announced the results of the Phase Ib/IIa clinical study of GZR18 Injection, in an obese/overweight population in China, at the American Diabetes Association's (ADA's) Scientific Sessions. The abstract entiltled "A Novel GLP-1 Analog, GZR18, Induced an 18.6% Weight Reduction in Subjects with Obesity in a Phase Ib/IIa Trial" was presented at the meeting on June 22, 2024.

Context

Gan & Lee announced that a multi-center, placebo-controlled, randomized, double-blind, 30-week Phase II clinical study evaluating the efficacy and safety of GZR18 injection in Chinese adults with obesity and overweight is in progress. A total of 338 adults with obesity or overweight were enrolled in this study, and the study explores a broader dose range and frequency of administration. The main body of the Phase II has now been completed, and the priliminary study data further support the results of the reported Phase Ib/IIa obese/overweight study, particularly the results achieved with bi-weekly dosing frequency.

In addition, Gan & Lee announced the results of preclinical trials of GZR4 and GZR101 at the ADA's Scientific Sessions.

Design

This randomized, double-blind, placebo-controlled, dose-escalation Phase Ib/IIa clinical study evaluated the safety, tolerability, pharmacokinetics and efficacy of GZR18 Injection in Chinese subjects with obesity/overweight after multiple administration on a once-weekly (QW) or bi-weekly (Q2W) dosing interval. A total of 36 obese participants were enrolled in the study and randomized in a 3:1 ratio to receive a dose titration of 1.5 mg to 30 mg of GZR18 Injection or a matching placebo for a total of 35 weeks.

Per the abstract, the study investigated the weight loss ability of GZR18 and evaluated the feasibility of administrating GZR18 at different frequencies and included a 31-week dose-escalation period. Upon dose escalation to 9 mg/week, subjects were divided into dosing sub-cohorts of QW or Q2W.

Endpoints

Per the abstract, endpoints were body weight change and AEs incidence.

Results

After 35 weeks of treatment, the mean weight change from baseline in the GZR18 QW group was -16.5 kg (95% CI: -19.9 kg, -13.1 kg); the placebo-adjusted mean percent weight change from baseline was -18.6% (95% CI: -25.5%, -11.6%). Although it was not a head-to-head study, when compared to
the published data on weight reduction of similar products currently available on the market, GZR18's weight-reducing ability outperformed semaglutide and dual-incretin receptor targeted tirzepatide in similar study duration. Meanwhile, the mean weight change from baseline in the GZR18 Q2W group was -11.3 kg (95% CI: -15.4 kg, -7.2 kg); the placebo-adjusted mean percent weight change from baseline was -13.5% (95% CI: -21.0%, -6.0%).

In addition, the percentage of participants achieving weight reductions of ≥5%, 10%, and 15% from baseline were 100.0%, 90.0%, and 80.0%, respectively, in the GZR18 QW group, and the percentage of participants achieving weight reductions of ≥5%, 10%, and 15% from baseline were 71.4%, 71.4%, and 42.9%, respectively, in the GZR18 Q2W group. No participant in the placebo group achieved a weight reduction of 5% and above.

Per the abstract, GZR18 reduced body weight and improved metabolic profiles in study participants. Its weight-loss effects surpassed those of semaglutide (2.4 mg) and tirzepatide (15 mg) in recent Phase III trials involving similar Chinese populations (-9.8% and -17.5%, respectively).

Most Common Adverse Events

In terms of safety, GZR18 Injection was well tolerated in obese participants. The most commonly reported adverse events (AE) during treatment were gastrointestinal related AEs, and all were mild to moderate in severity. This is consistent with the incretin-based therapies approved for the treatment of obesity and overweight and occurred mainly in the early dose-escalation period. There were no serious hypoglycemic events in this study and no serious adverse events related to the investigational drug.

Conclusion

The study results demonstrated efficacy of GZR18 Injection than placebo for weight reduction in Chinese obese subjects.

Comment

GLP-1 receptor agonist monotherapy remains an active area of interest owing to the broad range of cardiometabolic benefits the class can provide. Although combination therapies can offer greater efficacy, they also come with the potential for greater risks and increased costs.

The mean placebo-adjusted weight loss for GZR18 reached an impressive 18.6% in the weekly dosing group and 13.5% in every two weeks dosing group. The weekly administration was also associated with 80% of recipients achieving at least 15% weight loss. Moreover, lipid, glycemic, and blood pressure benefits were also reported for GZR18. GI AEs were reported most frequently (affecting more than 50% of recipients of the active treatment), mainly early in the treatment period, as is to be expected with the class, although no data on discontinaution rates was reported. With the weight loss efficacy for GZR18 being greater than that observed for semaglutide and tirzepatide in recent Phase III trials involving similar Chinese populations, further investigation of GZR18 appears to be warranted, with refinement of the titration approach to curb GI AEs.

Source:

PR Newswire 06/22/2024 (Gan & Lee)
American Diabetes Association (ADA) 06/22/2024 (Abstract 1858-LB)
Citeline Analysis

HRS9531 for Obesity

Event Date:	06/22/2024
Event Type:	Trial Data - Top-Line Results (Clinical Analysis)
Trial Name:	Phase II - HRS9531-201
Market Group:	Metabolic
Lead Company:	Jiangsu Hengrui Pharmaceuticals (600276:SS)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

Hengrui Pharmaceutical announced that data from Phase II study of HRS9531 was presented in late breaking abstract entitled "Efficacy and Safety of HRS9531, a Novel Dual GLP-1/GIP Receptor Agonist, in Obese Adults-A Phase 2 Trial" was presented at the American Diabetes Association (ADA) 84th Scientific Sessions on June 22, 2024.

Context

The authors of the study note a Phase III study with HRS9531 in Chinese overweight or obese individuals is already ongoing and multi-regional studies are being planned.

Design

In this randomized, double-blind, placebo-controlled phase II study, 249 Chinese adults with a BMI between 28 and 40 kg/m2 were randomly divided into five groups in a ratio of 1:1:1:1:1, and received once HRS9531-weekly subcutaneous injections (1.0 mg, 3.0 mg, 4.5 mg, and 6.0 mg) or placebo for 24 weeks. The primary endpoint was the percentage change from baseline in body weight at week 24.

Endpoints

The primary endpoint was the percentage change in body weight at week 24.

Results

The percent change in least squares mean (LS mean) in body weight in the HRS9531 subcutaneous 1.0 mg, 3.0 mg, 4.5 mg, and 6.0 mg groups at week 24 compared to baseline was -5.4% (95% CI: -7.3%, -3.5%), -13.4% (95% CI: -15.2%, -11.5%), -14.0% (95% CI: -15.9%, -12.1%), and -16.8%, respectively (95% CI: -18.8%, -14.9%) compared to -0.1% (95% CI: -2.1%, 1.8%) in the placebo group (P<0.0001 for all comparisons compared to placebo). The proportions of participants who lost ≥5% of their body weight were 52.0%, 88.2%, 92.0%, 91.8%, and 10.2%, respectively. In addition, HRS9531 was superior to placebo in lowering blood pressure, improving glycemic control, and lowering triglyceride levels. The change in LS mean from baseline to week 24 in systolic blood pressure ranged from -4.46 to -8.33 mmHg (-0.41 mmHg in the placebo group) in the HRS9531 group and -5.14 to -12.73 cm (-1.82 cm in the placebo group) in the HRS9531 group.

Most Common Adverse Events

No treatment-related serious adverse events occurred, and no treatment was discontinued due to treatment-related adverse events.

ConclusioN

HRS9531 can effectively reduce body weight, blood pressure, blood glucose and triglycerides, and has a good safety profile. These data will support further clinical development for HRS9531 for obesity treatment.

Comment

Jiangsu Hengrui Pharmaceuticals' HRS9531 is a novel dual GLP-1 and GIP receptor agonist that has already demonstrated weight loss efficacy in Phase I trials. Now, data from a placebo controlled Phase II trial of the asset for obesity are available. Almost 250 Chinese adults with a BMI of 28–40kg/m^2 were randomized to receive once-weekly subcutaneous injections of up to 6mg of HRS9531. The primary endpoint of mean percentage change in body weight at Week 24 was met, with a reduction of 16.8% for the top dose of HRS9531, compared to -0.1% with placebo. More than 90% of the participants receiving the top dose achieved ≥5% body weight reduction. HRS9531 also offered improvements over placebo for BP, glycemic control, and triglyceride levels. Most AEs were mild or moderate in severity, and the most common AEs were GI-related, occurring early in the treatment period. Further investigations into HRS9531 are warranted to asses its otneial for obesity and related metabolic indications.

Source:

American Diabetes Association (ADA) 06/22/2024 (Abstract 1861-LB)
PR Newswire 06/23/2024 (American Diabetes Association)
Press Release 06/26/2024 (Hengrui, Japanese)
Citeline Analysis

HS235 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	35Pharma
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	N/A
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Precision-Engineered Activin and GDF Ligand Trap HS235—A Novel Lean Mass–Preserving Treatment for Obesity" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Incretin mimetics have revolutionized the pharmacotherapy of obesity leading to unprecedented weight loss and improvement of cardiometabolic health. However, incretins reduce body mass in a non-selective manner. In obese patients treated with incretins, undesirable loss of lean body mass (LBM) can account for up to 40% of overall weight loss. Loss of LBM negatively impacts resting metabolic rate, leading to a weight loss plateau and often unsustainable results. LBM preservation is a desirable treatment goal for obesity pharmacotherapy and overall cardiometabolic health. Activins and growth differentiation factors (GDFs), members of the TGF-beta superfamily, are validated targets controlling body composition and metabolism. Specific and selective blockade of activins and GDFs represents a novel anti-obesity treatment strategy which can act orthogonally to incretins. HS235 is an activin receptor ectodomain-based Fc-fusion protein that has been rationally designed to attain optimal inhibition of ligands controlling body composition in obesity.

Methods

To validate the anti-obesogenic potential of HS235, diet-induced obese (DIO) mice were injected with HS235, an incretin mimetic, or a combination of both. Fat mass, LBM, muscle weights, and biomarker readouts were assessed at the end of study.

Results

In DIO mice, HS235 and the incretin mimetic significantly improved metabolic parameters and decreased fat mass, but only HS235 increased LBM, while incretin-based treatment led to LBM loss. Importantly, the addition of HS235 to the incretin mimetic lead to a synergistic fat mass loss and prevented loss of LBM.

Conclusions

Potent and selective inhibition of activins and GDFs by HS235 represents a novel LBM preserving weight loss strategy

orthogonal to incretin mimetics. This data supports the development of HS235 as a novel anti-obesity agent to complement currently approved incretin-based medications to improve quality of weight loss.

Comment

Activins and growth differentiation factors regulate body composition and metabolism, providing an array of therapeutic targets for metabolic diseases. HS235 is an activin receptor ectodomain-based Fc-fusion protein being developed by 35Pharma to improve body composition in obesity when administered with incretin-based therapies. As overactive activin signaling is also implicated in heart failure (HF), HS235 is also being investigated for obesity-related HF with preserved ejection fraction (HFpEF). In murine obesity models, HS235 significantly decreased fat mass, affecting visceral and subcutaneous fat, while increasing lean body mass. Importantly, when H235 was administered in combination with tirzepatide, there was synergistic fat loss but preservation of lean mass. In other murine HF models, HS235 reduced left ventricular systolic and diastolic blood pressures after four weeks. Moreover, exercise tolerance was improved in mice treated with HS235.

HS235 has the potential to be a treatment for HFpEF with obesity phenotype as well as improving body composition in patients receiving incretin-based therapies.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 298-OR)
Citeline Analysis

Retatrutide for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - 18122
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	60% (2% Above Avg.)
Average Approval:	58%

An abstract entitled "Effects of Triple-Hormone Receptor Agonist Retatrutide on Lipid Profiling in Participants with Obesity" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

In phase 2 (n=338), retatrutide (RETA), an agonist of GIP, GLP-1 and glucagon receptors, reduced body weight, fasting glucose, triglycerides (TG), LDL and VLDL cholesterol in participants with obesity. To understand changes in energy metabolism, lipidomic profiling was conducted.

Methods

Adult participants with obesity (BMI ≥30 kg/m2), or overweight (BMI ≥ 27 kg/m2) with a weight related comorbidity, were randomized to RETA 1, 4, 8, 12 mg or PBO for 48 wk. Fasting plasma collected at baseline, 24 and 48 wk, was used to measure acylcarnitines and complex lipid species using targeted mass spectrometry. Data were analyzed using a mixed model for repeated measures.

Results

An increase in 3-hydroxybutyrate (3-HB) was noted after 24 wk, accompanied by an increase in 3-hydroxybutyrylcarnitine (C4OH), acetylcarnitine-to-free carnitine ratio (C2/C0), and medium-chain ACs. The decrease of TGs at 48 wk was bias towards short-chain and saturated species. RETA 12 mg decreased total dihydroceramides (DhCers) at 48 wk by −20.1%, p-value <0.001. The increase in ketone body and C2/C0 observed after 24 wk is suggestive of adipose tissue lipolysis and reliance on fat oxidation.

Conclusions

Inverse changes in TGs and DhCers were observed which associate with improved insulin sensitivity, reduced hepatic steatosis and systemic inflammation. Evaluation of potential benefits on cardiovascular events and MASLD may merit further investigation.

Comment

This was a post-hoc analysis of a Phase II trial of non-diabetic patients with obesity or overweight in which doses of up to 12mg of retatrutide weekly were assessed over 48 weeks; the top dose required up-titration over the first 12 weeks of the trial period. In particular, the effects of glucagon on hepatic fatty acid oxidation were of interest. Lipidomic analysis was applied to fasting plasma lipid assessment taken at baseline and at 24 weeks and 48 weeks from 286 patients.

Retatrutide was associated with greater reduction in triglycerides of short carbon length, which are associated with increased risk for diabetes and insulin resistance. Measures of hepatic ketogenesis showed a dose response, with retatrutide suggesting a corresponding increase in hepatic fatty acid oxidations; a similar pattern was seen for biomarkers of mitochondrial beta oxidation of fatty acids. However, responses peaked at 24 weeks and then fell. This pattern correlated with weight loss at 24 weeks but not at 48 weeks. Measures of long-chain and medium-chain acylcarnitine accumulation suggested efficient fatty acid oxidation, and the increased ratio of medium to long chain measures for these parameters indicated increased insulin sensitivity and reduced CV risk. These lipid parameters suggest benefits for retatrutide in terms of hepatic steatosis and insulin sensitivity, both of which are linked to CV benefits, as well as reducing the chances of development of type 2 diabetes.

Discussions included questions on whether glucagon is essential for ketoacidosis, which may place some type 2 diabetes patients at risk, but as the patients in this trial were non-diabetics the presenter could not comment. However, data from the original study results indicated an increased risk for ketoacidosis was unlikely.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 117-OR)
Citeline Analysis

Retatrutide for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - 18122
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	60% (2% Above Avg.)
Average Approval:	58%

An abstract entitled "Retatrutide, an Agonist of GIP, GLP-1, and Glucagon Receptors, Improves Markers of Pancreatic Beta-Cell Function and Insulin Sensitivity" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Retatrutide (RETA), an agonist of GIP, GLP-1 and glucagon receptors, significantly reduced HbA1c up to 2.2% in T2D and body weight up to 17% in T2D at wk 36 and 24% in obesity without T2D (OB) at wk 48 in Ph2 trials.

Methods

To explore mechanisms by which RETA improved glycemic control, we assessed markers of beta-cell function and insulin sensitivity. Mixed models for repeated measures evaluated fasting biomarkers from two Ph2 double-blind randomized placebo-controlled trials: in T2D (281 subjects, 36-wks) and in OB (338 subjects, 48-wks).

Results

Homeostatic model assessment (HOMA2)-IR index (insulin), a measure of insulin resistance, decreased over time from baseline with RETA 12 mg reaching reductions of 39% in T2D at 36 wks and 52% in OB at 48 wks. Adiponectin, a marker of insulin sensitivity, increased with RETA from baseline up to 52% in T2D and up to 70% in OB, ($p<0.001$). HOMA2-B index (C-peptide), a marker of beta-cell function, rapidly increased with RETA up to 88% from baseline in T2D but did not significantly increase in OB. Proinsulin and proinsulin/C-peptide ratios, measures of beta-cell stress and dysfunction, decreased from baseline with RETA, by up to 71% and 62%, respectively, in T2D ($p<0.001$).

Conclusions

In conclusion, RETA improved markers of beta-cell function in T2D and markers of insulin sensitivity in T2D and OB.

Comment

Two Phase II double-blind, randomized, placebo-controlled trials assessed retatrutide in both patients with type 2 diabetes and overweight/obesity. The Phase II diabetes study enrolled 281 type 2 diabetes patients with HbA1c between 7% and 10.5% who had been treated with diet and exercise alone or with a stable dose of metformin for at least three months prior to screening. The primary outcome was change in HbA1c from baseline, and key secondary endpoints included change in body weight and change in fasting blood glucose. The other Phase II study enrolled 338 obese or overweight participants and utilized a primary endpoint of mean change in body weight from randomization to Week 24. Data from the Phase II trials showed that retatrutide significantly reduced HbA1c by up to 2.2% and body weight by up to 17% in type 2 diabetes patients at Week 36, and reduced body weight by 24% in obesity patients without type 2 diabetes at Week 48.

The analysis assessed markers of beta-cell function and insulin sensitivity to elucidate the mechanisms by which retatrutide improves glycemic control. Homeostatic model assessment (HOMA) 2-IR index, a marker of insulin resistance, decreased from baseline, with the highest dose (12mg) achieving the largest reductions. Specifically, retatrutide (12mg) produced reductions of 39% compared to 22% for placebo in type 2 diabetics at 36 weeks, and 52% compared to 12% in obese patients at 48 weeks. Assessment of beta-cell function through C-peptide showed that retatrutide increased HOMA2-B index by up to 88% from baseline in type 2 diabetes, but did not show a significant increase in obesity.

Overall, retatrutide appears to improve beta-cell function and insulin sensitivity in patients with type 2 diabetes and obesity. A question was asked about the correlation between weight loss and the insulin resistance reported, with a reply from Dr. Melissa Thomas that the linear pattern had not been explored but glycemic improvements occurred quickly, although the insulin sensitivity appeared to have a longer time course and further research was needed. Evidence indicates retatrutide improves markers of beta-cell function in type 2 diabetes and markers of insulin sensitivity in type 2 diabetes and obesity, suggesting that GIP/GLP-1/glucagon triple agonism is a potential valuable treatment option. Importantly, as glucagon can interfere with insulin action, these improvements in beta-cell function and insulin sensitivity may offset any interference and as such are playing a role in retatrutide's ability to produce exceptional glycemic control.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 266-OR)
Citeline Analysis

BGE-105 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	BioAge Labs, Inc.
Partner Companies:	Amgen (AMGN)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

BioAge Labs announced the preclinical data for azelaprag (BGE-105) in combination with incretin agonists for the treatment of obesity. The abstract entitled "The Apelin Receptor Agonist Azelaprag Increases Weight Loss in Diet-Induced Obese Mice on Incretin Agonists and Restores Body Composition and Muscle Function to That of Lean Controls" was presented at the American Diabetes Association's 84th Scientific Sessions on June 21, 2024.

Context

In a Phase Ib trial, azelaprag promoted muscle metabolism and prevented muscle atrophy in healthy older volunteers on bed rest. The study also showed that azelaprag shifted circulating protein biomarkers in a manner consistent with its function as an exercise mimetic, increasing predicted resting energy expenditure and cardiorespiratory fitness. The Company plans to initiate a Phase II trial in mid-2024 evaluating azelaprag in combination with tirzepatide (Zepbound) in older adults with obesity. The study is being conducted in collaboration with Eli Lilly and Company, which is providing tirzepatide, and Lilly's Chorus clinical development organization, which is advising on trial design and execution.

Design

Per the abstract, high fat diet-induced obese (DIO) mice were treated for 20 days with incretin agonists, with or without azelaprag. Food and water intake, serum glucose and protein levels, body composition (via EchoMRI), and grid hang latency were measured.

Results

In a mouse model of obesity, the addition of azelaprag to the GLP-1/GIP receptor agonist tirzepatide increased total weight loss to 39%, approximately double that of tirzepatide monotherapy, restoring body weight to the range observed in lean control mice. The combination restored body composition and muscle function to that of lean controls. Similar results were observed when azelaprag was combined with semaglutide. The synergistic weight loss observed in animals on combination therapy was not due to a further decrease in food intake.

Per the abstract, DIO mice on tirzepatide (10 nmol/kg) lost 16% of body weight, while mice on tirzepatide+azelaprag (1.1 g/L) lost 39%, bringing body weight in range of lean controls. Combined treatment also improved body composition:

DIO/tirzepatide mice had lean mass 60% of body weight, vs. 69% for DIO/tirzepatide+azelaprag and 70% for lean controls. Grid hang assays showed that azelaprag fully restored muscle function to that of lean controls (latency, 79 sec): DIO/tirzepatide, 38 sec; DIO/tirzepatide+azelaprag, 86 sec.

Conclusion

These preclinical data highlight the ability of azelaprag to improve the weight loss and metabolic benefits of incretin therapy, the current standard of care for obesity.

Comment

Azelaprag (BGE-105; AMG 986) is an oral small molecule agonist of the apelin receptor (APJ) in development by BioAge Labs for use in conjunction with incretin-based therapies to reduce weight and improve body composition. This asset mimics the action of apelin, an endogenous peptide released in response to exercise, increasing energy expenditure. In early preclinical and clinical trials, apelin was positively corelated with function and longevity and with reduced muscle atrophy in older adults, with relatively higher protein synthesis contributing. Protein homeostasis with azelaprag matched that seen following exercise.

Now, obesity murine models showed approximately twice the weight loss observed for tirzepatide and semaglutide when combined with azelaprag versus monotherapy, with similar caloric intake. Addition of azelaprag to tirzepatide showed a return to the body composition of lean controls in a dose-dependent manner. Trials with semaglutide and tirzepatide are planned in the STRIDES program, looking primarily at weight loss and also body composition.

Discussions following the presentation included a question on the potential for increase in temperature, but no such adverse outcomes were observed, and confirmation that diabetes control is also to be investigated. Another question regarding CV AEs due to the expression of apelin in heart and vascular tissues was answered with no such reports from studies thus far and a reminder that muscle, including cardiac muscle, is not increased but rather returned to lean control levels. Based on these data, the company hopes to develop an oral azelaprag-incretin combination treatment offering the efficacy of injectable competitors.

Source:

Business Wire 06/21/2024 (BioAge)
American Diabetes Association (ADA) 06/21/2024 (Abstract 118-OR)
Citeline Analysis

Mazdutide for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase II - (China)
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Innovent Biologics (1801)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	25% (Same As Avg.)
Average Approval:	25%

An abstract entitled "A Phase 2 Study of Mazdutide 9 mg in Chinese Adults with BMI of 30 kg/m2 or more" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

To evaluate the efficacy and safety of 9 mg mazdutide, a once-weekly GLP-1 and glucagon receptor dual agonist, in Chinese participants with obesity.

Methods

In a randomized, double-blind, placebo-controlled phase 2 trial (NCT04904913), 80 Chinese adults with a BMI of 30 kg/m2 or more (mean baseline body weight: 96.9 kg; mean baseline BMI: 34.3 kg/m2) were randomized to receive once-weekly, subcutaneous mazdutide 9 mg (n=60) or placebo (n=20) for 24 weeks. Subsequently, participants voluntarily chose to participate in an extended 24-week double-blind treatment period. The primary endpoint was the percentage change in weight from baseline at week 24.

Results

At week 24, mean percentage change in weight from baseline were −13.3% (SE 0.8) with mazdutide 9 mg and 2.1% (1.5) with placebo (estimated treatment difference: −15.4% [95%CI: −18.8, −12.0], P <0.0001); 81.7%, 65.0% and 31.7% of participants with mazdutide achieved weight reduction of 5% or more, 10% or more, and 15% or more, respectively, while no participant with placebo achieved weight reduction of 5% or more. Furthermore, compared with placebo, greater improvements were observed with mazdutide at week 24 in multiple cardiometabolic risk factors, most notably in triglycerides (−43.5% with mazdutide, −1.7% with placebo), alanine aminotransferase (−32.8%, 12.7%) and serum uric acid (−102.2 μmol/L, −16.1 μmol/L). In participants with baseline liver fat content (as measured by MRI-PDFF) of 5% or more, the liver fat content was reduced by 73.3% after 24-week treatment of mazdutide. Mazdutide 9 mg was well tolerated, with no adverse event leading to treatment discontinuation reported. The most frequently reported adverse events were gastrointestinal, and most were mild to moderate in severity.

Conclusions

In Chinese adults with a BMI of 30 kg/m2 or more, mazdutide 9 mg showed robust body weight reduction and prominent hepatic benefits.

Comment

Following on from the efficacy demonstrated with 6mg doses of mazdutide, a 9mg dose was evaluated over up to 48 weeks in a Phase II trial involving 80 obese patients in China. The primary endpoint was change in weight from baseline at Week 24, with a mean placebo-adjusted weight loss of 11.2%. At the same time point, the proportions of mazdutide 9mg recipients achieving weight loss of at least 5%, 10%, 15%, or 20% were 81.7%, 65.0%, 31.7%, and 21.7%, respectively. Greater benefits on these endpoints were achieved at Week 48, particularly for attaining weight loss of at least 15% or 20%. Impressive liver fat reuction were reported and overall, cardiometabolic benefits and safety data aligned with results from the GLORY-1 Phase III trial. Overall, these data suggest that a higher dose of mazdutide (9mg) would be worth evaluating in Phase III trials considering the additional efficacy without worsening safety or tolerability.

Based on these data for mazdutide, Chinese approval for obesity is on the horizon, and Eli Lilly will be hoping that a similar risk-benefit profile is demonstrated in studies that could lead to approvals in other major pharmaceutical markets for obesity and other metabolic indications.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1866-LB)
Citeline Analysis

Mazdutide for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - GLORY-1 (China)
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Innovent Biologics (1801)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	25% (Same As Avg.)
Average Approval:	25%

An abstract entitled "Efficacy and Safety of Mazdutide in Chinese Participants with Overweight or Obesity (GLORY-1)" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

To evaluate the efficacy and safety of mazdutide, a once-weekly GLP-1 and glucagon receptor dual agonist, in Chinese participants with overweight or obesity.

Methods

In this phase 3 randomized, double-blind, placebo-controlled trial (NCT05607680), we assigned 610 Chinese adults with a BMI of 28 kg/m2 or more, or 24 kg/m2 or more and at least one weight-related comorbidity, in a 1:1:1 ratio to receive once-weekly, subcutaneous mazdutide 4 mg, 6 mg or placebo for 48 weeks. Co-primary endpoints were the percentage change in weight from baseline and a weight reduction of 5% or more at week 32.

Results

At baseline, the mean body weight was 87.2 kg, the mean BMI was 31.1 kg/m2, and 83.1% of participants had a BMI of 28 kg/m2 or more. Mazdutide met co-primary endpoints and all key secondary endpoints, demonstrating superiority to placebo on body weight changes, weight-loss targets, and improvements on multiple cardiometabolic risk factors (Table). Mazdutide was well tolerated, with adverse events leading to treatment discontinuation reported in 1.5% of participants with mazdutide 4 mg, 0.5% with mazdutide 6 mg and 1.0% with placebo. The most frequently reported adverse events were gastrointestinal, mostly mild to moderate in severity.

Conclusions

In Chinese adults with overweight or obesity, mazdutide provides significant reductions in body weight and cardiometabolic risk factors.

Comment

Mazdutide (IBI362; LY3305677) is a once-weekly GLP-1 and glucagon receptor dual agonist from Eli Lilly and Innovent Biologics in development for type 2 diabetes and obesity. GLORY-1 is a Phase III trial that assessed the efficacy and safety of mazdutide in more than 600 Chinese participants with overweight or obesity. Participants received subcutaneous mazdutide 4mg or 6mg or placebo weekly for 48 weeks. For the co-primary endpoint of percentage change in weight from baseline, the mean weight loss after Week 32 was 11.0% for mazdutide 4mg and 13.4% for the 6mg dose; placebo was associated with a mean weight loss of 0.2%. The other co-primary endpoint, weight reduction of 5% or more at Week 32, was achieved by 76.3%, 84.0%, and 10.9% of individuals in the mazdutide 4mg, mazdutide 6mg, and placebo groups, respectively. Weight loss of at least 15% was achieved by 27.7% and 44.0% of individuals in the mazdutide 4mg and 6mg groups, respectively. Significant reductions in waist circumference were also reported with the active treatment, as well as significant improvements in lipid profiles, blood pressure, and liver function parameters. Discontinuation rates were low, with the most common AEs being GI-related, a known effect of this drug class.

These impressive results not only demonstrate the efficacy of mazdutide, but also suggest that its activity improves central adiposity as well as providing broader cardiometabolic benefits.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1856-LB)
Citeline Analysis
Citeline Analysis

Mazdutide for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - GLORY-1 (China)
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Innovent Biologics (1801)
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	25% (Same As Avg.)
Average Approval:	25%

An abstract entitled "Improvement of Liver Steatosis by Mazdutide in Chinese Participants with Overweight or Obesity—An Exploratory Analysis of GLORY-1" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

To explore the effect of mazdutide, a once-weekly GLP-1 and glucagon receptor dual agonist, on liver steatosis.

Methods

In the GLORY-1 phase 3 trial (NCT05607680), 610 Chinese adults with a BMI of 28 kg/m2 or more, or 24 kg/m2 or more and at least one weight-related comorbidity were randomly assigned 1:1:1 to receive once-weekly, subcutaneous mazdutide 4 mg, mazdutide 6 mg or placebo for 48 weeks. A subpopulation of participants had MRI scan and liver fat content (LFC) measurement by MRI-proton density fat fraction (MRI-PDFF). Change from baseline at week 48 in LFC was an exploratory endpoint of the study.

Results

In participants with baseline LFC of 5% or more and 10% or more, treatment with mazdutide 4 mg or 6 mg for 48 weeks led to marked and dose-dependent reductions in LFC. Of note, a mean relative reduction of 80.2% was achieved with mazdutide 6 mg among participant with baseline LFC of 10% or more. In participants with baseline LFC of 5% or more, compared with placebo, substantially more participants with mazdutide 4 mg and 6 mg achieved ≥30% relative reduction in LFC, ≥50% relative reduction in LFC and normalization of LFC (<5%) at week 48 (Figure).

Conclusions

In Chinese adults with overweight or obesity and liver steatosis, mazdutide 4 mg and 6 mg provides robust reductions in LFC.

Comment

Metabolic-associated fatty liver disease (also known as NAFLD) is a common co-morbidity in patients with type 2 diabetes and obesity, as well as having overlapping pathophysiology. Data from 69 patients with baseline liver fat content (LFC) of ≥5% (based on magnetic resonance imaging-proton density fat fraction [MRI-PDFF]) in the GLORY-1 trial, including 25 who received mazdutide 4mg, 22 who received mazdutide 6mg, and 22 who received placebo, were analyzed. Mazdutide 4mg and 6mg were associated with relative reductions in liver fat of 63.3% and 73.2%, respectively, whereas placebo was associated with a relative increase of 8.2%. The percentage of patients achieving at least a 30% reduction in LFC was 80.0%, 95.5%, and 27.3% in the mazdutide 4mg, mazdutide 6mg, and placebo groups, respectively. Significant improvements in alanine transaminase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) versus placebo were also demonstrated for both the mazdutide doses. These data suggest that mazdutide could have the potential to treat MAFLD, or metabolic-associated steatohepatitis (MASH; also known as NASH).

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1857-LB)
Citeline Analysis

Mounjaro for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - SURMOUNT-2
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Effect of Tirzepatide on Kidney Function in People with Excess Body Weight and Type 2 Diabetes—A Post-Hoc Analysis of the SURMOUNT-2 Trial" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Tirzepatide (TZP), a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, has shown kidney protective effects in people with type 2 diabetes (T2D) at high risk for cardiovascular disease. In the SURMOUNT-2 (SM-2) trial in people with obesity or overweight with T2D, at 72 weeks TZP significantly reduced body weight by up to 15.7%, HbA1c by 2.22%, and systolic and diastolic blood pressure by 7.7mmHg and 2.9mmHg respectively.

Methods

This post-hoc analysis assessed the potential impact of TZP vs PBO on kidney parameters in SM-2 trial participants. Data from all participants randomly assigned to treatment were included (pooled TZP [10 and 15 mg], N = 623; PBO, N = 315). Assessments included CKD-EPI creatinine-cystatin-C-based eGFR (Cr-Cys-C-eGFR), and urine albumin-to-creatinine ratio (UACR). The change from baseline to week 72 was analyzed using mixed models for repeated measures with on-treatment data.

Results

Baseline mean Cr-Cys-C-eGFR was 91.3±19.5 mL/min/1.73m2. The estimated treatment difference (ETD) between pooled TZP groups and PBO on the change from baseline in Cr-Cys-C-eGFR was 0.0 mL/min/1.73m2 (95% confidence interval [CI] -1.7, 1.7; p=0.993). TZP compared to placebo did not change Cr-Cys-C-eGFR at week 72 in participants with baseline Cr-Cys-C-eGFR <60 ml/min/1.73m2 (p=0.180) or ≥ 60 ml/min/1.73m2 (p=0.714). Baseline median UACR was 13.0 mg/g (interquartile range 6.0-35.0 mg/g). UACR significantly decreased with TZP vs. PBO (ETD -31.1 %, 95% CI -40.9, -19.7, p<0.001) and for those with baseline UACR ≥30 mg/g, the ETD was -55.2% (95% CI -68.5, -36.4; p<0.001).

Conclusions

In this SM-2 trial population of participants with obesity or overweight with T2D and preserved eGFR at baseline, TZP reduced albuminuria without adversely affecting eGFR.

Comment

This post-hoc analysis of data from the SURMOUNT-2 trial demonstrated renoprotective effects in people with type 2 diabetes at high risk for CV disease. This new post-hoc analysis assessed the potential impact of tirzepatide on kidney parameters in patients with type 2 diabetes and obesity or overweight. At baseline, approximately 20% of patients were receiving an SGLT-2 inhibitor and around 55% were taking a renin-angiotensin-aldosterone system (RAAS) inhibitor.

Over the 72-week trial period, the changes in CKD-EPI creatinine-cystatin-C-based eGFR (Cr-Cys-C-eGFR) were comparable for the placebo- and tirzepatide-treated patients. There was no correlation between body weight change and eGFR in either group. There was a significant 31.1% reduction in albuminuria in the tirzepatide groups compared to the placebo group, which increased to more than 50% when evaluating patients with baseline UACR ≥30mg/g. Tirzepatide was associated with a greater proportion of patients having normal albuminuria after treatment than placebo (60.4% vs. 54.9%). A discussant questioned the impact of SGLT-2 inhibitor use, with the reply being that there was very little difference to the results with or without this drug class.

The mechanisms for tirzepatide's benefit on kidney outcomes will be explored further in the TREASURE-CKD trial of patients with obesity with or without type 2 diabetes.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 264-OR)
Citeline Analysis

Mounjaro for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase III - SURMOUNT-2
Market Group:	Metabolic
Lead Company:	Eli Lilly and Company (LLY)
Partner Companies:	Mitsubishi Tanabe Pharma
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	100% (Same As Avg.)
Average Approval:	100%

An abstract entitled "Efficacy of Tirzepatide in Achieving the Composite Endpoints of Glycemic, Blood Pressure, and Lipid Goals in SURMOUNT-2" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

In the SURMOUNT-2 (SM-2) trial of adults with overweight/obesity and type 2 diabetes (T2D), tirzepatide (TZP), a once weekly GIP/GLP-1 receptor agonist, significantly reduced body weight (BW) in conjunction with a reduced calorie diet and increased physical activity.

Methods

This post-hoc analysis assessed the proportion of participants achieving composite endpoints of BP <130/80 mm Hg, non-HDL <130 mg/dl, and three HbA1c thresholds of <7%, < 6.5% and <5.7% at 72 weeks. Logistic regression with missing value imputed by mixed model repeated measures, using the efficacy estimand, assessed participants who achieved the composite endpoints, in the 10mg (N=312) or 15mg (N=311) TZP groups, versus placebo (PBO) (N=315).

Results

Overall baseline mean BW was 100.7 kg, BMI 36.1kg/m2, HbA1c 8.02%, BP 130.5/79.8 mm Hg and non-HDL 132.5 mg/dl. For 15mg TZP, 33.8%, 32.8%, and 25.9% of participants achieved the composite endpoints versus 7.5%, 3.9%, and 0.7% of PBO at 72 weeks. Findings for the TZP 10mg group were similar to those observed in the 15mg group. In people with T2D and overweight/obesity, higher proportion of participants receiving TZP achieved clinically meaningful composite endpoints, which included BP, lipids and HbA1c goals compared to PBO.

Conclusions

This suggests that TZP can help achieve multiple clinical goals, in addition to meaningful weight loss, important for improving cardiometabolic health.

Comment

The SURMOUNT-2 trial showed that tirzepatide was effective for reducing body weight in obese patients with type 2 diabetes. This post-hoc analysis showed that significantly higher proportions of the tirzepatide10mg and 15mg groups achieved the triple goal versus placebo. Although post-hoc analyses should be interpreted with caution, this analysis indicates that there are broader cardiometabolic benefits from tirzepatide irrespective of dose or baseline BMI. Discussants asked questions regarding what is driving the benefit, the BP or the lipid reduction. Professor Naveed Sattar, the presenter, replied that the data suggested lipid and BP control was already quite good, so therefore the glycemic control was probably the main driver. Another question was the use of lipid-modifying therapies and antihypertensive medications in the study population, which might have impacted the results, but this was not assessed.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 120-OR)
Citeline Analysis

GSBR-1290 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase Ib/IIa - GSBR-1290-02
Market Group:	Metabolic
Lead Company:	Structure Therapeutics, Inc. (GPCR)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	25% (Same As Avg.)
Average Approval:	25%

An abstract entitled "A Phase 1b/2a Study of the Safety and Tolerability of GSBR-1290, a Novel Oral Small Molecule Glucagon-Like Peptide 1 Receptor Agonist (GLP-1RA), in Healthy Overweight/Obese Volunteers (HOV) and Participants with Type 2 Diabetes Mellitus (T2DM)" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

GSBR-1290 is a novel, oral, non-peptide GLP-1RA and a potential alternative to injectable or oral peptides used for the treatment of T2DM and obesity. These studies were designed to evaluate the safety, tolerability, and efficacy of GSBR-1290.

Methods

Phase 1b: The safety and tolerability of multiple ascending doses of GSBR-1290 (5-90mg) and its effects on body weight (BW) were investigated in 24 HOV over 4 weeks. Phase 2a: The effects of GSBR-1290 on safety, tolerability, HbA1c, glucose, and BW were investigated in 54 participants with T2DM (45 and 90mg) over 12 weeks and in an interim 8-week analysis of 40 HOV (120mg).

Results

Phase 1b: There were no study discontinuations (d/c) due to adverse events (AEs). Most AEs were mild and GI-related, consistent with GLP-1RAs. BW was significantly reduced (up to 4.9% placebo-adjusted, p=0.013) over 4 weeks. Phase 2a T2DM: Two participants d/c from the study due to an AE (1 attributed to study drug: 2.8% d/c rate). Placebo-adjusted HbA1c (45 mg: -1.01%, p=0.008; 90 mg: -1.02%, p=0.001), BW (45 mg: -3.51%, p=0.0019; 90 mg: -3.26%, p=0.0013), and plasma glucose (45 mg: -2.70, p=0.01; 90 mg: -2.50, p=0.0008) were significantly reduced at day 84. Phase 2a Obesity: There were no study d/c due to AEs. Placebo-adjusted BW decreased though day 56 (120 mg: -4.74%; p<0.0001). Complete 12-week results from the cohort of 24 additional participants will be available at presentation. For all phase 2a, AEs were mild-moderate and GI-related, with no SAEs related to GSBR-1290. Conclusions: GSBR-1290 demonstrated favorable safety and tolerability in this Phase 1b/2a study in participants with T2DM and in HOV. GSBR-1290 demonstrated

clinical benefits in lowering BW, blood glucose, and HbA1c. These data provide clinical proof-of-concept of GSBR-1290 and support further clinical development in T2DM and obesity.

Conclusions

GSBR-1290 demonstrated favorable safety and tolerability in this Phase 1b/2a study in participants with T2DM and in HOV. GSBR-1290 demonstrated clinical benefits in lowering BW, blood glucose, and HbA1c. These data provide clinical proof-of-concept of GSBR-1290 and support further clinical development in T2DM and obesity.

Comment

Structure Therapeutics GSBR-1290 is an oral, small molecule, selective GLP-1 RA in development for Obesity. The Phase Ib portion of the study assessed the safety and tolerability of multiple ascending doses and effects on body weight in 24 HOV. No discontinuations due to adverse events (AEs) were observed and most AEs were mild and gastrointestinal (GI)-related, as expected with GLP-1 agonism. Significant reductions in body weight of up to 4.9% were achieved over four weeks. In the Phase IIa assessment, placebo-adjusted body weight decreased though day 56, with the highest dose (120mg) achieving a reduction of 4.74% ($p<0.0001$). These results have further established the safety, tolerability, and efficacy of GSBR-1290 and its potential as an alternative to injectable or oral peptides used for obesity. However, this was a relatively small study, and as such longer-term data from a Phase IIb 36-week obesity study using a tablet formulation are eagerly awaited. The Company plans to initiate a 36-week Phase 2b obesity study of GSBR-1290 in Q4 2024.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 767-P)
Citeline Analysis

GL0034 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Sun Pharmaceutical Industries Ltd. (SUNP)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	15% (Same As Avg.)
Average Approval:	15%

An abstract entitled "GL0034 (Utreglutide), a Novel GLP-1RA, Increases Liver FGF-21 and Demonstrates Significant Efficacy on Weight Loss, HbA1c, and Triglycerides in db/db Mice" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Glucagon-like peptide receptor agonists (GLP-1RA) stimulate fibroblast growth factor (FGF-21) production and both have overlapping metabolic effects like glycemic control, suppression of food consumption, and body weight reduction. GL0034 has demonstrated excellent safety and tolerability in phase 1 trials. Further, a single dose of subcutaneous administration of GL0034 in individuals with obesity resulted in 3.3 kg of weight loss that was sustained till day 22

Methods

We explored a fixed dose (21nM/kg) of GL0034, semaglutide (Sema) and tirzepatide (TZP) given to db/db mice every third day for 4 weeks. Biomarkers were measured on days 14 and 28.

Results

GL0034 increased liver FGF-21 and, uncoupling protein-1 (UCP-1) in brown and white adipose tissues significantly more than Sema and similarly to TZP. The effects of GL0034 on HbA1c (↓), insulin (↑), glucagon (↓), weight loss (↑), triglycerides (↓), and cholesterol (↓) were similar to those induced by Sema and TZP. Food consumption was similar to TZP and lower than with Sema (Table).

Conclusions

In conclusion, GL0034 shows robust efficacy on multiple metabolic parameters and may serve as a promising new super GLP-1RA for individuals with obesity +/- type 2 diabetes and for the treatment of MASLD with enhanced therapeutic benefits partly due to increased liver FGF-21.

Comment

In this murine model, GL0034 was compared to placebo as well as semaglutide and tirzepatide, both of which target GLP-1 and have been widely approved for type 2 diabetes and obesity. Mice were injected every third day for four weeks.

Day 14 measurements showed significant increases in insulin with all active treatments and corresponding reductions in HbA1c, with GL0034 achieving numerically better results. Repeated assessments on Day 28 showed greater benefits, particularly for GL0034. GL0034 achieved the greater reduction in body weight at Day 14 of 6.7% versus 3.1% and 5.5% for semaglutide and tirzepatide, respectively, although, interestingly, its impact on food consumption was less than that of tirzepatide at the same time point. Day 28 measures showed corresponding increases in benefits following the same patterns, with GL0034 reaching 7.9% weight loss versus 3.4% and 6.3% for semaglutide and tirzepatide, respectively.

Glucagon levels were lower with GL0034 than with the other active comparators on Day 28, and measurements of fibroblast growth factor (FGF)-21, which is being explored for its impact on body weight via interaction with GLP-1, showed that GL0034 achieved greater increases than semaglutide or tirzepatide. Higher levels of uncoupling protein 1 in brown adipose tissue were observed with GL0034 than for the active comparators, suggesting increased burning of fat via this pathway may be contributing to the efficacy of GL0034. Assessments of lipid levels also favored GL0034 numerically versus semaglutide and tirzepatide.

The data suggest that GL0034 offers superior weight loss compared to molecules already on the market, with weight loss driven by more than just reduced food consumption, and should these data be replicated in human trials, GL0034 could be a challenger for best in class.

Discussions included the potency of the drug, which was variable, while it was also noted that tirzepatide does not stimulate GIP receptors in mice, making it a less favorable comparator. The UCP-1 data suggest increased energy expenditure not seen with GLP-1 receptor agonists in humans, but these data are awaited.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 116-OR)
Citeline Analysis

GL0034 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase I - MAD Healthy Individuals
Market Group:	Metabolic
Lead Company:	Sun Pharmaceutical Industries Ltd. (SUNP)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	15% (Same As Avg.)
Average Approval:	15%

Sun Pharmaceutical presented results from a Phase I study of GL0034 (Utreglutide) in obese adults at the Scientific Sessions of the American Diabetes Association (ADA). The abstract entitled "Safety, Tolerability, and Metabolic Effects of Once-Weekly GL0034 (Utreglutide) in Individuals with Obesity—A Multiple Ascending Dose Study" was presented at the meeting on June 21, 2024.

Data from this study were last seen in June 2023.

Design

The Phase I multiple ascending-dose study evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of GL0034 (Utreglutide) in obese adults. Healthy, obese male participants (n=24; Age 18-40; BMI ≥ 28 kg/m²) were enrolled into a fixed-dose Cohort 1 (4 x 680 µg) or an increasing-dose Cohort 2 (680/900/1520/2000 µg) and assigned to treatment groups in a 3:1 ratio, receiving 4 weekly doses of either GL0034 or a placebo. An oral glucose tolerance test (OGTT) was performed on Day -1 (baseline) and Day 23 (after the 4th dose). The study was conducted in Belgium.

Results

The results were as follows:

- Body weight reduction was observed from baseline at Day 29 and persisted through Day 43 in treatment cohorts compared to placebo.
  - Absolute weight loss change of –4.6 ± 1.5 ($p<0.001$) in Cohort 2.
- Both cohorts showed reductions in glucose AUC0-120 min during OGTT on Day 23 and dose-dependent insulin AUC0-120 min reductions, suggesting improved insulin sensitivity.
- HbA1c, leptin levels, and lipid levels (triglycerides, total cholesterol, non-HDL cholesterol) were reduced in the treatment cohorts.

GL0034 administered once-weekly confirmed weight loss and improved gluco-metabolic parameters over a 4-week treatment period in individuals with obesity, even in the lowest dosing regimen

Per the abstract, in cohorts 1 & 2, body weight (BW) reduction versus baseline (BL) was 2.9 kg and 4.6 kg respectively on Day 29.

Most Common Adverse Events

GL0034 was well-tolerated with no treatment-related discontinuations. The most common adverse events were gastrointestinal, consistent with the incretin class profile.

Per the abstract, most common adverse events (AE) were gastrointestinal (GI) with dose-dependent nausea, decreased appetite and vomiting. One individual with a GI related serious AE rapidly recovered upon treatment with intravenous rehydration.

Conclusion

The Phase I study results have demonstrated weight loss, metabolic improvements, a favorable tolerability profile, and an ability to lower lipid profiles, especially triglycerides, suggesting an additional therapeutic benefit.

Comment

GL0034 has already demonstrated weight loss over more than three weeks in a single ascending dose trial in obese patients. In this trial, men with overweight or obesity were enrolled to assess either four doses of 680mcg of GL0034 (total dose of 2.72mg) or a regimen of 680mcg, followed by 900mcg, then 1,520mcg, and then 2,000mcg (total dose of 5.1mg) versus placebo. Oral glucose tolerance tests showed significant benefits for GL0034 versus placebo in terms of AUC assessments for glucose, as well as reductions in insulin, suggesting an increase in insulin sensitivity associated with the drug candidate. Small but significant reductions in HbA1c were reported for the active treatment groups but not for placebo despite normal mean HbA1c at baseline; there were no hypoglycemic episodes reported.

Weight loss at Day 29, approximatively a week after dosing completed, showed reductions of 2.9kg and 4.6kg for the steady dose group and ascending dose groups, respectively (placebo was associated with a 0.8kg weight loss); at Day 43, the steady dose group had weight loss of 1.4kg but the ascending dose group still had weight loss of 3.7kg; these data translated to weight reductions of around 1kg/mg of dose after four weeks. Both dose groups achieved significant reductions in leptin versus baseline, and the ascending dose group also achieved almost 50mg/dL reductions in TG levels on Day 23. GI AEs were the most common, consistent with the class, but were relatively high, affecting more than 80% of participants.

Overall, these early data suggest GL0034 has demonstrated enough for further clinical development for type 2 diabetes, obesity, and NASH. Discussions regarding the presentation included concerns over the high rate of GI AEs, with the presenter, Dr. Rajamannar Thennati, noting that titration will be employed in further trials.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 121-OR)
PR Newswire 06/22/2024 (Sun Pharmaceutical)
Citeline Analysis

TERN-501 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Terns Pharmaceuticals, Inc. (TERN)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	N/A
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

Terns Pharmaceuticals presented preclinical results of TERN-501 in combination with a GLP-1 receptor agonist for obesity at the American Diabetes Association (ADA) 84th Scientific Sessions. The abstract entitled "TERN-501 Enhances Weight Loss Efficacy of a GLP-1R Agonist in Obese Mice via Increased Fat Mass Loss without Additional Loss of Lean Mass" was presented at the meeting on June 23, 2024.

Design

Preclinical study in mice fed a high fat diet for 24 weeks prior to study start. Obese mice were treated once daily with vehicle, TERN-501, semaglutide, TERN-501+semaglutide, or tirzepatide for six weeks.

Per the abstract, male C57BL/6JRj mice were fed high fat diet (60% HFD) for 24 weeks prior to study start. Mice (~55 g BW) were treated once daily with vehicle, TERN-501 (6 mg/kg PO), semaglutide (sema, 30 nmol/kg SQ), or 501+sema for up to 6-weeks at thermal neutrality. Body weight and food intake were measured daily. Body composition was assessed by EchoMRI and EE was measured in metabolic chambers.

Results

The combination of TERN-501+semaglutide significantly enhanced weight loss compared to semaglutide alone. Additionally, the TERN-501+semaglutide combination showed proportionally greater loss of fat mass relative to lean mass compared to semaglutide alone, indicating improved quality of weight loss.

The study also explored metabolic adaptation, a counter regulatory process that decreases energy expenditure and limits the magnitude and sustainability of weight loss. Mice treated with semaglutide and tirzepatide showed significant weight loss that was associated with decreases in energy expenditure. When TERN-501 was combined with semaglutide, weight loss-induced lowering of energy expenditure was prevented and increases in the thermogenesis marker, UCP-1, were observed in subcutaneous adipose tissue. TERN-501 has possibility to attenuate metabolic adaptation and normalize energy expenditure, which may enhance the weight loss efficacy of GLP-1 therapies.

Per the abstract, TERN-501 significantly enhanced the weight loss efficacy of sema (-26% vs -33%, p<0.05) with increased fat mass loss (-11.8 g vs -15.2 g, p<0.05) without additional loss of lean mass. In contrast, the effect of TERN-501 alone on body weight was similar to vehicle (-1.6% vs 1.5%, p>0.05). In mice with higher initial body weight, 501+sema resulted in an additional 17% body weight loss vs sema alone.

Conclusion

TERN-501 significantly improved the efficacy of a GLP-1 receptor agonist by normalizing energy expenditure, resulting in greater weight loss, increased fat mass loss and relative preservation of lean mass.

Comment

The weight loss efficacy of drugs targeting the GLP-1 receptor is driven in part by reduced appetite, but the body can compensate as a result by reducing energy expenditure (EE). As the thyroid hormone receptor beta (THRβ) regulates EE, Terns Pharmaceuticals' TERN-501, a THRβ agonist, was assessed alone and in combination with semaglutide to evaluate its potential for improving body composition in a murine model. Results showed that the combination of TERN-501 plus semaglutide offered significantly greater weight loss efficacy than semaglutide monotherapy (-26% vs. -33%, respectively) plus greater fat mass loss (-11.8g vs. -15.2g, respectively) without additional loss of lean mass. Using metabolic chambers, TERN-501 was shown to mitigate the lower EE observed with semaglutide. These data suggest TERN-501 may be of benefit for optimizing body composition in the setting of GLP-1 receptor agonist-induced weight loss. This drug candidate shows promise for improving body composition and the potential for use either in combination with dedicated weight loss agents or as monotherapy, depending on the clinical need.

Source:

Globe Newswire 06/21/2024 (TERN)
American Diabetes Association (ADA) 06/23/2024 (Abstract 760-P)
American Diabetes Association (ADA) 06/23/2024 (Poster 760-P)
Citeline Analysis

XW004 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase I - SCW0503-1011 (Australia)
Market Group:	Metabolic
Lead Company:	Sciwind Biosciences Co., Ltd.
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	0% (Same As Avg.)
Average Approval:	N/A

An abstract entitled "Phase 1 Topline Safety, Efficacy, and Pharmacokinetics of Oral Ecnoglutide" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Ecnoglutide is a cAMP-biased, long-acting glucagon-like peptide 1 receptor agonists (GLP-1RA) being developed for the treatment of type 2 diabetes mellitus and obesity. Oral ecnoglutide (XW004) is formulated with an absorption enhancer, PNAC (T2026). The objective of this study was to evaluate the safety and tolerability of oral ecnoglutide in healthy adults.

Methods

We conducted a randomized, double-blind, placebo-controlled Phase 1 study in healthy (Cohorts 1 to 3) and healthy obese (Cohort 4) adults. Participants (n = 56) were randomized to receive oral ecnoglutide at target doses of 7, 15, or 30 mg QD for up to 6 weeks, with dose escalation. Safety, tolerability, PK, and body weight were assessed. The results of Cohorts 1 to 4 are presented, the study is ongoing to evaluate additional dosing schemes.

Results

Oral ecnoglutide was generally safe and well tolerated. The most common AEs were mild to moderate gastrointestinal events that occurred during dose escalation. There were no serious AEs. One participant experienced a Grade 3 AE of diarrhea that led to study drug discontinuation. At baseline, participants had a mean BMI of 25.8 to 26.1 kg/m2 (Cohorts 1 to 3) and 32.9 kg/m2 (Cohort 4). At end of treatment, participants in Cohorts 1 to 3 receiving up to 7, 15, or 30 mg QD oral ecnoglutide for 2 weeks had body weight change from baseline of -3.63, -3.38, and -6.55%, respectively vs -0.85% for placebo. Participants in Cohort 4 receiving up to 30 mg QD for 6 weeks had a body weight reduction of -6.76% vs -0.85% for placebo. At steady state, oral ecnoglutide 30 mg QD resulted in a plasma AUC0-24h of 12,470 h*ng/mL and calculated weekly AUC 0-168h of 87,290 h*ng/mL.

Conclusions

Oral ecnoglutide was safe and well tolerated and resulted in pronounced weight loss after 6 weeks of dosing. Improved oral

bioavailability enables a daily dose of 30 mg oral ecnoglutide to match or exceed the plasma exposure of weekly subcutaneous GLP-1 analogs. Oral ecnoglutide has a potential to be a best-in-class oral GLP-1RA.

Comment

Oral ecnoglutide (XW004) is a cyclic adenosine monophosphate (cAMP)-biased GLP-1 peptide analog in development for type 2 diabetes and obesity by Sciwind Biosciences. This formulation combines the peptide with an oral absorption enhancer agent that prevents degradation in the GI tract and increases absorption. A once-daily oral product could allow more people to benefit as well as opening up a different range of mechanisms of action that could be complementary.

This randomized, double-blind, placebo-controlled Phase I study involved healthy (Cohorts 1–3) and healthy obese (Cohort 4) adults who received oral ecnoglutide at target doses of 7mg, 15mg, or 30mg once daily for up to six weeks. After six weeks, the top dose of oral ecnoglutide was associated with a mean 6.6% reduction in weight versus a 0.9% loss for placebo in the healthy cohorts. The top dose recipients in Cohort 4 achieved a body weight reduction of 6.8% compared with a 0.9% loss for placebo. The most common AEs were mild to moderate, GI-related, and occurred during dose escalation, early in the treatment period. One subject discontinued treatment following grade 3 diarrhea.

The rapid efficacy and enhanced oral bioavailability of oral ecnoglutide suggest this asset has the potential to be an important new option for obesity, should larger clinical trials demonstrate similar results.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1871-LB)
Citeline Analysis

S-309309 for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Preclinical Results (Clinical Analysis)
Trial Name:	Preclinical Studies
Market Group:	Metabolic
Lead Company:	Shionogi & Co. Ltd. (4507)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	25% (Same As Avg.)
Average Approval:	25%

An abstract entitled "S-309309, a Novel MGAT2 Inhibitor, Enhances Intestinal Fatty Acid Beta Oxidation and Provides Metabolic Benefits in DIO Mice" was presented at the American Diabetes Association Annual Meeting on June 21, 2024.

Data in this event has been created solely from the abstract program.

Background

Pharmacological inhibition of Monoacylglycerol acyltransferase 2 (MGAT2) suppresses the food intake and the gain of body weight in high fat diet (HFD)-induced obesity (DIO) mice. However, the effects on metabolic abnormalities associated with obesity and detailed mechanisms of action remain unknown. In this study, we investigated the metabolic effects of S-309309, a novel selective MGAT2 inhibitor, in DIO mice and the involvement of energy consumption in the anti-obesity effects of S-309309.

Methods

Mice were fed a HFD for 4 weeks to establish a DIO model. S-309309 (3 mg/kg, b.i.d.) was orally administered to DIO mice for 13 weeks. Daily body weight and weekly food intake were recorded until Week 4, and parameters of glucose and lipid metabolism were measured on Week 12. Additionally, under pair-feeding conditions, S-309309 (3 mg/kg, b.i.d.) was orally administered to DIO mice for 6 weeks with recording daily body weight. Energy expenditure was measured during the first 7 days of S-309309 treatment, and gene expression analysis was performed 4 days after the treatment.

Results

S-309309 suppressed food intake and body weight gain in DIO mice over the course of the study. DIO mice treated with S-309309 also showed decreases in insulin resistance index, hepatic triglycerides content, plasma alanine aminotransferase and aspartate aminotransferase level, and gene expression related to fibrosis. Furthermore, S-309309 suppressed body weight gain under pair-feeding conditions with enhanced energy expenditure and upregulation of intestinal gene expression related to long-chain fatty acid beta oxidation.

Conclusions

S-309309 enhanced beta oxidation in the intestine and increased energy expenditure in DIO mice. Also, S-309309

improved insulin sensitivity and fatty liver. Taken together, these results suggest that S-309309 may be a promising anti-obesity drug that improves metabolism with multiple mechanisms of action.

Comment

Monoacylglycerol acyltransferase (MGAT) 2 is an enzyme involved in the regulation of triglyceride absorption and homeostasis. Shionogi's S-309309 is an MGAT2 inhibitor in Phase II development for obesity. Overall, administration of S-309309 was associated with suppression of food intake and limiting of body weight gain as well as decreases in insulin resistance and hepatic triglyceride content and improvements in liver function parameters in murine models. These data support further development of S-309309 for obesity and other metabolic diseases.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 1649-P)
Citeline Analysis

Trevogrumab for Obesity

Event Date:	06/21/2024
Event Type:	Trial Data - Updated Results (Clinical Analysis)
Trial Name:	Phase I - R2477-1033-HV-1621
Market Group:	Metabolic
Lead Company:	Regeneron Pharmaceuticals, Inc. (REGN)
Partner Companies:	N/A
Former Companies:	N/A
Change to Likelihood of Approval:	0%
Likelihood of Approval:	25% (Same As Avg.)
Average Approval:	25%

The abstract entitled "The Effect of Combined Activin A and Myostatin Blockade on Body Composition—A Phase 1 Trial" was presented at the American Diabetes Association (ADA) conference on June 21, 2024.

Data summarized in this event is solely based on data contained in the abstract from the ADA website. Citeline was unable to obtain updated data, if any, from the actual presentation at the ADA conference.

Data from this study were last seen in January 2018.

Design

This Phase I, double-blind, placebo-controlled study randomized healthy males and postmenopausal females to single-dose or multiple-dose parts of the study. For single-dose, females received: trevogrumab 6 mg/kg (n=6); garetosmab 10 mg/kg (n=6); combination trevogrumab 6 mg/kg and garetosmab (1 mg/kg, n=6; 3 mg/kg, n=6; 10 mg/kg, n=12); or placebo (PBO; n=12). For multiple-dose, females received: garetosmab 10 mg/kg every 4 weeks (Q4W; n=6) or PBO (n=2); combination trevogrumab 6 mg/kg and garetosmab 10 mg/kg every 2 weeks (n=6) or PBO (n=4). In the multiple dose part, males received garetosmab 10 mg/kg Q4W (n=8) or PBO (n=8).

Results

Thigh muscle volume (TMV) increased from baseline 7.7% with trevogrumab 6 mg/kg + garetosmab 10 mg/kg (nominal *P*<0.001 vs PBO) and 4.6% with trevogrumab 6 mg/kg (nominal *P*<0.05 vs PBO) 8 weeks after single-dose. Total fat mass and android fat mass (AFM) decreased from baseline with trevogrumab 6 mg/kg + garetosmab 10 mg/kg (-4.6% and -6.7%; both nominal *P*<0.05 vs PBO). After multiple-dose, TMV initially increased after 3 doses of trevogrumab 6 mg/kg + garetosmab 10 mg/kg but decreased to similar levels as PBO at Week 28; AFM and visceral fat mass decreased from baseline by 14.3% and 20.1%, respectively (both nominal *P*<0.05 vs PBO). No safety concerns were identified in any active treatment groups.

Conclusion

Combined administration of trevogrumab and garetosmab led to dose-dependent, greater-than-additive increases in TMV and lean mass, while decreasing fat mass in healthy participants.

Comment

Regeneron's trevogrumab and garetosmab are monoclonal antibodies targeting myostatin signaling and activin A, AB, and AC signaling, respectively, which restrict muscle growth. In this placebo-controlled, randomized Phase I trial involving healthy males and postmenopausal females, single and multiple doses of trevogrumab and garetosmab monotherapy and the combination were assessed. At eight weeks after single doses, thigh muscle volume (TMV) was significantly increased from baseline by 7.7% with the combination of trevogrumab and garetosmab, and by 4.6% with trevogrumab monotherapy. Total fat mass and android fat mass (AFM) decreased by 4.6% and 6.7% from baseline, respectively, with the combination. After three doses of the combination, TMV initially increased, but by Week 28 had reduced to placebo levels; reductions from baseline of 14.3% in AFM and 20.1% in visceral fat mass were noted. No safety concerns were reported for the active treatments. Ways of preserving or even improving body compostion are generating increasing interest in the obesity research space, with trevogrumab worthy of further investigation.

Source:

American Diabetes Association (ADA) 06/21/2024 (Abstract 34-OR)
Citeline Analysis

BIOMEDTRACKER
CITELINE COMMERCIAL

List of Biomedtracker ADA Events

Event Date	Drug	Lead Company	Ticker	Event Type	Trial Name	Link
Cachexia / Weight Loss						
06/22/2024	NA-931	Biomed Industries, Inc.		Trial Data - Preclinical Results	Preclinical Studies	524963
06/21/2024	Enobosarm	Veru Inc.	VERU	Trial Data - Updated Results	Phase IIb - Cancer Wasting|Phase III - POWER1|Phase III - POWER2	526313
06/21/2024	Enobosarm	Veru Inc.	VERU	Trial Data - Updated Results	Phase IIb - Cancer Wasting|Phase III - POWER1|Phase III - POWER2	526315
Chronic Kidney Disease (CKD)						
06/21/2024	HM15275	Hanmi Pharmaceutical Co., Ltd.	128940	Trial Data - Preclinical Results	Preclinical Studies	526358
Cushing's Syndrome						
06/24/2024	Korlym	Corcept Therapeutics Incorporated	CORT	Trial Data - Updated Results	Phase IV - CATALYST	521842
Diabetes Mellitus, Type I						
06/23/2024	SAB-142	SAB BIO	SABS	Trial Data - Preclinical Results	Preclinical Studies	521779
06/23/2024	BioVascular Pancreas	Humacyte, Inc.	HUMA	Trial Data - Preclinical Results	Preclinical Studies	522018
06/22/2024	Afrezza	MannKind Corporation	MNKD	Trial Data - Subgroup Analysis	Phase IV - INHALE-3	521699
06/22/2024	HFG1	HighField Biopharmaceuticals		Trial Data - Preclinical Results	Preclinical Studies	521804
06/22/2024	GZR101	Gan & Lee Pharmaceuticals		Trial Data - Preclinical Results	Preclinical Studies	521921
06/21/2024	VX-880	Vertex Pharmaceuticals Incorporated	VRTX	Trial Data - Updated Results	Phase I/II - Open Label	521717
06/21/2024	MTX-101 (Mozart)	Mozart Therapeutics, Inc.		Trial Data - Preclinical Results	Preclinical Studies	521728
06/21/2024	Awiqli	Novo Nordisk A/S	NVO	Trial Data - Updated Results	Phase III - ONWARDS-6	526321
06/21/2024	Mounjaro	Eli Lilly and Company	LLY	Trial Data	Phase IV – Real-World Studies	526325
Diabetes Mellitus, Type II						
06/23/2024	HR-17031	Jiangsu Hengrui Pharmaceuticals	600276:SS	Trial Data - Top-Line Results	Phase II - 26-week Study	522107
06/22/2024	NA-931	Biomed Industries, Inc.		Trial Data - Preclinical Results	Preclinical Studies	524964
06/22/2024	GZR101	Gan & Lee Pharmaceuticals		Trial Data - Preclinical Results	Preclinical Studies	521750
06/22/2024	KO-539	Kura Oncology, Inc.	KURA	Trial Data - Preclinical Results	Preclinical Studies	521926
06/22/2024	HFG1	HighField Biopharmaceuticals		Trial Data - Preclinical Results	Preclinical Studies	521805
06/22/2024	GZR-4	Gan & Lee Pharmaceuticals		Trial Data - Preclinical Results	Preclinical Studies	521872
06/21/2024	TLC-6740	OrsoBio, Inc.		Trial Data - Preclinical Results	Preclinical Studies	521892
06/21/2024	TLC-3595	OrsoBio, Inc.		Trial Data - Preclinical Results	Preclinical Studies	521903
06/21/2024	MLX-0871	Biolex Therapeutics, Inc.		Trial Data - Preclinical Results	Preclinical Studies	521756

06/21/2024	Omnipod 5	Insulet Corporation	PODD	Trial Data - Top-Line Results	SECURE-T2D	521700
06/21/2024	Soliqua 100/33	Sanofi	SNY	Trial Data	Phase IV – Real-World Studies	526316
06/21/2024	Soliqua 100/33	Sanofi	SNY	Trial Data - Updated Results	Phase III - LPS17396 (China)	526317
06/21/2024	Awiqli	Novo Nordisk A/S	NVO	Trial Data - Updated Results	Phase III - ONWARDS 2|Phase III - ONWARDS 3|Phase III - ONWARDS-4|Phase IIIa - ONWARDS 1|Phase IIIa - ONWARDS-5	526318
06/21/2024	Awiqli	Novo Nordisk A/S	NVO	Trial Data - Updated Results	Phase III - ONWARDS 2|Phase III - ONWARDS 3|Phase III - ONWARDS-4|Phase IIIa - ONWARDS 1|Phase IIIa - ONWARDS-5	526319
06/21/2024	Awiqli	Novo Nordisk A/S	NVO	Trial Data - Updated Results	Phase III - ONWARDS 2|Phase III - ONWARDS 3|Phase III - ONWARDS-4|Phase IIIa - ONWARDS 1|Phase IIIa - ONWARDS-5	526320
06/21/2024	Awiqli	Novo Nordisk A/S	NVO	Trial Data - Updated Results	Phase III - ONWARDS 2|Phase III - ONWARDS 3|Phase III - ONWARDS-4|Phase IIIa - ONWARDS 1|Phase IIIa - ONWARDS-5	526322
06/21/2024	Awiqli	Novo Nordisk A/S	NVO	Trial Data - Updated Results	Phase III - ONWARDS 2|Phase III - ONWARDS 3|Phase III - ONWARDS-4|Phase IIIa - ONWARDS 1|Phase IIIa - ONWARDS-5	526323
06/21/2024	HMS5552	Hua Medicine (Shanghai) Ltd.	2552	Trial Data - Updated Results	Phase I - Cross-over Study	526324
06/21/2024	HD-6277	Hyundai Pharm Co., Ltd	A004310	Trial Data - Updated Results	Phase II - HT-006-02 (Korea)	526336
06/21/2024	HTD1801	HighTide Therapeutics Inc.	2511	Trial Data - Updated Results	Phase II - T2DM+NAFLD (China)	526337
06/21/2024	Retatrutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase II - vs. Dulaglutide	526338
06/21/2024	Mounjaro	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase IIIb - SURPASS-6 (vs. Insulin Lispro)	526328
06/21/2024	Mounjaro	Eli Lilly and Company	LLY	Trial Data	Phase IV – Real-World Studies	526329
06/21/2024	Mounjaro	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase III - SURPASS-5 (w/Basal Insulin)|Phase IIIb - SURPASS-6 (vs. Insulin Lispro)	526330
06/21/2024	Mounjaro	Eli Lilly and Company	LLY	Trial Data	Phase IV – Real-World Studies	526331
06/21/2024	Efsitora alfa	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase I - I8H-MC-BDCI (Germany)	526332
06/21/2024	GSBR-1290	Structure Therapeutics, Inc.	GPCR	Trial Data - Updated Results	Phase Ib/IIa - GSBR-1290-02	526350
06/21/2024	ZT002	Beijing QL Biopharmaceutical Co.,Ltd		Trial Data - Top-Line Results	Phase I - SAD	526352
06/21/2024	HS-20094	Hansoh Pharmaceutical Group Company Limited	3692	Trial Data - Top-Line Results	Phase II - HS-20094-201 (China)	526354
06/21/2024	ATR-258	Atrogi		Trial Data - Preclinical Results	Preclinical Studies	526355
06/21/2024	GLY-200	Glyscend Therapeutics, Inc.		Trial Data - Updated Results	Phase II - Double Blind Study	526341
06/21/2024	GLY-200	Glyscend Therapeutics, Inc.		Trial Data - Updated Results	Phase II - Double Blind Study	526342
06/21/2024	GLY-200	Glyscend Therapeutics, Inc.		Trial Data - Updated Results	Phase II - Double Blind Study	526343
06/21/2024	GL0034	Sun Pharmaceutical Industries Ltd.	SUNP	Trial Data - Preclinical Results	Preclinical Studies	526346
06/19/2024	Envlo	Daewoong Pharmaceutical Company Ltd.	A069620	Trial Data - Retrospective Analysis	Phase III - ENHANCE-M (w/Metformin)|Phase III - w/ Metformin (China)|Phase III - w/Metformin & Gemigliptin	521444
Diabetic Nephropathy						
06/24/2024	Ozempic	Novo Nordisk A/S	NVO	Trial Data - Final Results	Phase III - FLOW	521914
Fibrodysplasia Ossificans Progressiva (FOP)						

06/21/2024	Garetosmab	Regeneron Pharmaceuticals, Inc.	REGN	Trial Data - Updated Results	Phase I - w/Trevogrumab	524971
Non-Alcoholic Steatohepatitis (NASH)						
06/23/2024	ZT-003	Beijing QL Biopharmaceutical Co.,Ltd		Trial Data - Preclinical Results	Preclinical Studies	524959
06/22/2024	Pemvidutide	Altimmune Inc.	ALT	Trial Data - Updated Results	Phase I - 12-Week Study (NAFLD)	521732
Obesity						
06/24/2024	ARO-INHBE	Arrowhead Pharmaceuticals, Inc.	ARWR	Trial Data - Preclinical Results	Preclinical Studies	521857
06/24/2024	ZP8396	Zealand Pharma A/S	ZEAL	Trial Data - Preclinical Results	Preclinical Studies	524965
06/24/2024	ZP8396	Zealand Pharma A/S	ZEAL	Trial Data - Updated Results	Phase Ia - SAD (Healthy Volunteers)|Phase Ib - MAD (Healthy Volunteers)	524966
06/23/2024	ZT-003	Beijing QL Biopharmaceutical Co.,Ltd		Trial Data - Preclinical Results	Preclinical Studies	524958
06/23/2024	SRK-439	Scholar Rock, LLC	SRRK	Trial Data - Preclinical Results	Preclinical Studies	521891
06/23/2024	Pemvidutide	Altimmune Inc.	ALT	Trial Data - Updated Results	Phase II - MOMENTUM	521738
06/23/2024	Mazdutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase III - GLORY-1 (China)	521794
06/23/2024	Rejuva	Fractyl Health	GUTS	Trial Data - Preclinical Results	Preclinical Studies	521701
06/22/2024	DA-1726	NeuroBo Pharmaceuticals, Inc.	NRBO	Trial Data - Preclinical Results	Preclinical Studies	521713
06/22/2024	GZR18	Gan & Lee Pharmaceuticals		Trial Data - Top-Line Results	Phase Ib/IIa - Adult Patients in Obese/Overweight (China)	521739
06/22/2024	Mazdutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase III - GLORY-1 (China)	521900
06/22/2024	PG-102	ProGen Co. Ltd		Trial Data - Preclinical Results	Preclinical Studies	524960
06/22/2024	PG-102	ProGen Co. Ltd		Trial Data - Top-Line Results	Phase I - SL-MG12-P1	524961
06/22/2024	NA-931	Biomed Industries, Inc.		Trial Data - Preclinical Results	Preclinical Studies	524962
06/22/2024	BMS-986089	Biohaven Ltd.	BHVN	Trial Data - Preclinical Results	Preclinical Studies	524967
06/22/2024	HRS9531	Jiangsu Hengrui Pharmaceuticals	600276:SS	Trial Data - Top-Line Results	Phase II - HRS9531-201	521731
06/21/2024	Zepbound	Eli Lilly and Company	LLY	Trial Data - Final Results	Phase III - SURMOUNT-OSA	525600
06/21/2024	Trevogrumab	Regeneron Pharmaceuticals, Inc.	REGN	Trial Data - Updated Results	Phase I - R2477-1033-HV-1621	524969
06/21/2024	Mazdutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase II - (China)	526333
06/21/2024	Mazdutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase III - GLORY-1 (China)	526334
06/21/2024	Mazdutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase III - GLORY-1 (China)	526335
06/21/2024	Retatrutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase II - 18122	526339
06/21/2024	Retatrutide	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase II - 18122	526340
06/21/2024	TLC-6740	OrsoBio, Inc.		Trial Data - Updated Results	Phase I - SAD/MAD (NZ)	521730
06/21/2024	BGE-105	BioAge Labs, Inc.		Trial Data - Preclinical Results	Preclinical Studies	521724
06/21/2024	GL0034	Sun Pharmaceutical Industries Ltd.	SUNP	Trial Data - Updated Results	Phase I - MAD Healthy Individuals	521727

06/21/2024	TERN-501	Terns Pharmaceuticals, Inc.	TERN	Trial Data - Preclinical Results	Preclinical Studies	521707
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06/21/2024	Zepbound	Eli Lilly and Company	LLY	Trial Data - Updated Results	Phase III - SURMOUNT-2	526356
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Urinary Incontinence						
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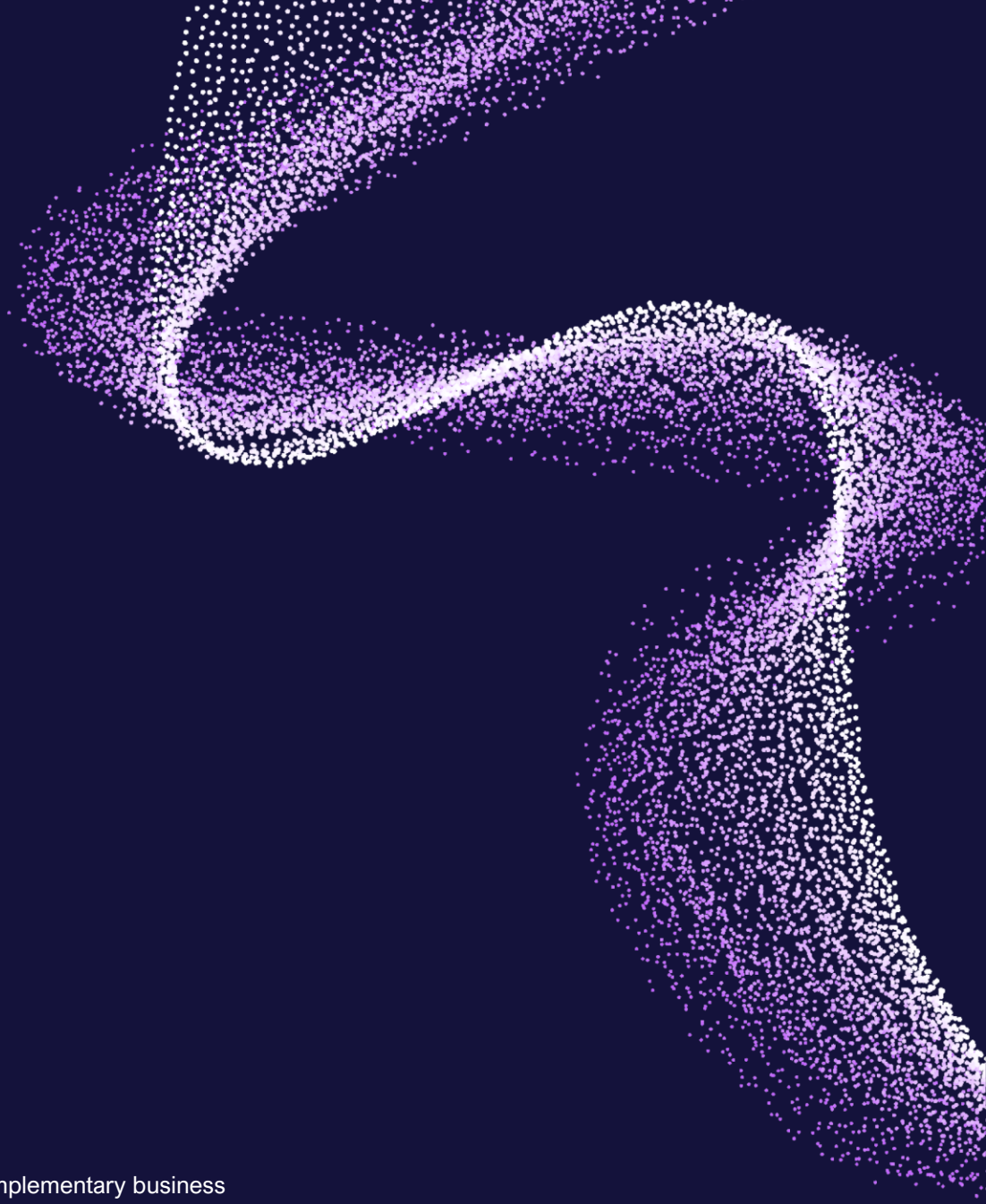

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