Overview
Harmony is the global Phase III clinical trial program for Tanzeum (albiglutide), a product developed by GSK for the treatment of type 2 diabetes. The comprehensive program comprised eight individual studies (Harmony 1 to Harmony 8) with primary endpoints at 26 weeks, 32 weeks, 1 or 2 years. Together the trials involved more than 5,000 patients, over 2,000 of whom received Tanzeum, totalling 7,500 patient-years of overall program exposure.

Study Design
The Harmony program evaluated Tanzeum alone or in combination with or against commonly-used classes of type 2 diabetes treatment, including insulin, in patients diagnosed with diabetes and at different stages of the disease, as well as those with renal impairment.
- The primary efficacy point for all studies was the change from baseline in HbA1c, a parameter indicative of the average blood glucose concentration over the course of three months, compared to placebo or active comparators. These active comparators included standard anti-diabetic medications including another GLP-1 receptor agonist, sulphonylureas, thiazolidinediones, insulin (basal and prandial) and dipeptidyl peptidase 4 (DPP-4) inhibitors.
- Secondary endpoints included change from baseline in fasting plasma glucose and weight as well as the proportion of patients achieving glycemic goals.

Harmony Program Summary 1-12

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<th>Trial</th>
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<th>Comparator &amp; dosage</th>
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| Harmony 1 1,2,3 | Tanzeum as add-on to thiazolidinedione vs. placebo | 52-week primary endpoint | Randomized double-blind, placebo-controlled study | Patients inadequately controlled on a regimen of pioglitazone with or without metformin received either 30mg Tanzeum or placebo | - At the 52-week primary endpoint, treatment with Tanzeum achieved a significantly greater reduction in HbA1c from baseline compared to placebo (-0.8% for Tanzeum versus -0.1% for placebo, p<0.05).  
- There was no significant difference in weight change from baseline to week 52 between Tanzeum and placebo-treated subjects. The between group treatment difference was -0.2kg (p=0.7193) at week 52 (Change from baseline for Tanzeum +0.3kg and placebo +0.5kg). |
| Harmony 2 1,4 | Tanzeum mono-therapy vs. placebo | 52-week primary endpoint | Randomized double-blind, placebo-controlled study | Patients inadequately controlled on diet and exercise received either Tanzeum (30mg and 50mg) or placebo | - At 52 weeks, both Tanzeum doses demonstrated statistically significant HbA1c reductions from baseline compared to placebo (treatment difference versus placebo -0.8% 30mg Tanzeum; -1.0% 50mg Tanzeum; p<0.05).  
- At 52 weeks, patients on Tanzeum as well as on placebo reduced weight (-0.4kg, -0.9kg and -0.7kg for Tanzeum 30mg, Tanzeum 50mg, and placebo respectively). The treatment difference was not significant for any of the treatment groups. |
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| Harmony 3 1,2,5 | Tanzeum as add-on to metformin vs. placebo, sulphonylurea or sitagliptin | 104-week primary endpoint | Randomized double-blind, placebo- and active-controlled, parallel-group study | Patients inadequately controlled on metformin received either Tanzeum (30mg, if necessary uptitrated to 50mg), placebo, sitagliptin (100mg) or glimepiride (2-4mg) | • At 104 weeks, Tanzeum achieved a significantly greater reduction from baseline HbA1c compared to all comparators (p<0.05). The mean treatment difference was -0.9% vs placebo, -0.4% vs sitagliptin and -0.3% vs glimepiride.  
• Patients on Tanzeum, sitagliptin and placebo reduced weight from baseline, while patients on glimepiride increased weight (-1.2kg, -0.9kg, -1.0kg and +1.2kg for Tanzeum, sitagliptin, placebo and glimepiride). The treatment difference between Tanzeum and glimepiride (-2.4kg) was statistically significant (p<0.05). |
| Harmony 4 1,2,6 | Tanzeum vs. insulin glargine (basal insulin) | 52-week primary endpoint | Randomized open-label, active-controlled study | Patients on metformin with or without a sulphonylurea received Tanzeum or daily insulin glargine (Note: ~82% of subjects were on met + SU) | • At 52 weeks both groups achieved a similar reduction from baseline in HbA1c (-0.7% and -0.8% in the Tanzeum and insulin glargine groups). Non-inferiority criteria were met.  
• Patients on Tanzeum lost weight (-1.1kg) while those on insulin glargine experienced weight gain (+1.6kg) and the treatment difference (-2.6kg) was statistically significant (p<0.05). |
| Harmony 5 1,2,7 | Tanzeum as add-on to metformin plus sulphonylurea vs. placebo or pioglitazone | 52-week primary endpoint | Randomized double-blind study | Patients currently on a background therapy of metformin and glimepiride received either Tanzeum, placebo or pioglitazone  
Both pioglitazone and Tanzeum were uptitrated according to clinical need | • At 52 weeks, the reduction from baseline in HbA1c in the Tanzeum group was statistically significant versus the placebo group (treatment difference for Tanzeum versus placebo was -0.9%; p<0.05). However, the change from baseline HbA1c in the Tanzeum group did not meet the non-inferiority criteria compared to pioglitazone.  
• Patients on Tanzeum and placebo lost weight from baseline (-0.4kg in both groups), while patients on pioglitazone experienced weight gain (+4.4kg). The treatment difference (-4.9kg) in weight between Tanzeum and pioglitazone was statistically significant (p<0.05). |
| Harmony 6 1,8,9 | Tanzeum as add-on to insulin lispro (basal insulin) vs. insulin lispro (mealtime insulin) | 26-week primary endpoint | Randomized open label, active-controlled study | Patients inadequately controlled on intermediate or long-acting insulin received either Tanzeum or insulin lispro, each administered in combination with long-acting insulin glargine  
Tanzeum and both insulins were uptitrated according to clinical need  
(Note: OADs Met, TZDs and α-glucosidase inhibitors were allowed during treatment) | • At 26 weeks, both the Tanzeum and insulin lispro groups achieved clinically and statistically significant reductions in HbA1c from baseline (reduction of -0.8% vs -0.6% in the Tanzeum and insulin lispro groups respectively). Non-inferiority criteria were met.  
• Treatment with Tanzeum at 26 weeks resulted in a mean weight loss for Tanzeum (-0.7 kg) compared to a mean weight gain for insulin lispro (+0.8 kg) and the difference between treatment groups was statistically significant. |
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<td>Harmony 7</td>
<td>Tanzeum as add-on to metformin or sulphonylurea or thiazolidinedione vs. liraglutide</td>
<td>32-week primary endpoint</td>
<td>Open-label, active-controlled, parallel-group study</td>
<td>Patients received either Tanzeum (30mg once-weekly, automatically uptitrated to 50mg at week 6) or liraglutide (0.6mg once-daily, automatically titrated to 1.2mg at week 2 and 1.6mg at week 3)</td>
<td>• At 32 weeks, change in HbA1c was -0.8% and -1% in the Tanzeum and liraglutide groups respectively. However, non-inferiority criteria were not met. • Patients on Tanzeum and liraglutide lost weight. However, the weight loss for patients receiving Tanzeum (-0.6kg) was lower than that observed with liraglutide (-2.2kg) at week 32. The treatment difference was +1.55kg in favour of liraglutide (p&lt;0.05).</td>
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<td>Harmony 8</td>
<td>Tanzeum in patients with renal impairment</td>
<td>26-week primary endpoint</td>
<td>Randomized double-blind, active-controlled, parallel-group study</td>
<td>Tanzeum compared to a DPP-4 inhibitor, sitagliptin (25mg, 50mg or 100mg for severe, moderate and mild renal impairment), in type 2 diabetes patients with mild-severe renal impairment. Patients randomised were failing on diet/exercise or metformin, thiazolidinedione, sulphonylurea, or any combination (metformin stopped if eGFR &lt; 60 mL/min)</td>
<td>• At 26 weeks, Tanzeum showed statistically significant reductions in HbA1c from baseline compared to sitagliptin (-0.8% for Tanzeum and -0.5% for sitagliptin, p&lt;0.05 for the treatment difference.) • Both treatment groups reduced weight (-0.8kg and -0.19kg for Tanzeum and sitagliptin respectively); however, the magnitude of change was greater with Tanzeum at week 26. The treatment difference (-0.6kg) was statistically significant (p&lt;0.05).</td>
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**Indications and Usage**

TANZEUM is a GLP-1 receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

**Limitations of Use:**
- Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.
- Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis.
- Not for patients with pre-existing severe gastrointestinal disease.
- Has not been studied in combination with prandial insulin.
Important Safety Information**

BOXED WARNING: RISK OF THYROID C-CELL TUMORS

Thyroid C-cell tumors have been observed in rodent studies with glucagon-like peptide-1 (GLP-1) receptor agonists at clinically relevant exposures. It is unknown whether Tanzeum causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Tanzeum is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

WARNINGS AND PRECAUTIONS

Pancreatitis: Discontinue promptly if suspected. Do not restart if confirmed. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia: Can occur when used in combination with insulin secretagogues (e.g. sulfonylureas) or insulin. Consider lowering sulfonylurea or insulin dosage when starting Tanzeum.

Hypersensitivity Reactions: Discontinue Tanzeum if suspected. Monitor and treat promptly per standard of care until signs and symptoms resolve.

Renal Impairment: Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Macrovascular Outcomes: There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with Tanzeum or any other antidiabetic drug.

ADVERSE REACTIONS

Adverse reactions, reported in ≥10% of patients treated with Tanzeum and more frequently than in patients on placebo, were upper respiratory tract infection, diarrhea, nausea, and injection site reaction.

[**For all information regarding safety and warnings please refer to the Prescribing Information for Tanzeum]
References

1 Tanzeum EU Summary of Product Characteristics, GlaxoSmithKline 2014.
3 Reusch J, et al. HARMONY 1 Week 52 Results: Albiglutide vs. Placebo in Patients with Type 2 Diabetes Mellitus not Controlled On Pioglitazone ± Metformin. Data presented at ADA 2013, Abstract number: 2013-57-LB.
4 Nauck M, et al. HARMONY 2 Wk 52 Results: Albiglutide Monotherapy in Drug Naïve Patients with Type 2 Diabetes Mellitus. Data presented at ADA 2013, Abstract number: 2013-55-LB.
5 Ahren B, et al. HARMONY 3. 104 Week (Wk) Efficacy of Albiglutide (Albi) Compared to Sitagliptin (Sita) and Glimepiride (SU) in Patients (pts) with Type 2 Diabetes Mellitus (T2DM) on Metformin (Met)., Data presented at ADA 2013, Abstract number: 2013-52-LB.
6 Pratley R, et al. HARMONY 4: 52-Wk Efficacy of Albiglutide (Alb) vs. Insulin Glargine (Glar) in Patients (pts) with T2DM., Data presented at ADA 2013, Abstract number: 2013-54-LB.