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TTP399, a Liver-Selective Glucose Kinase Activator (GKA), Lowers Glucose and Does NOT Increase Lipids in Subjects with Type 2 Diabetes Mellitus (T2DM)

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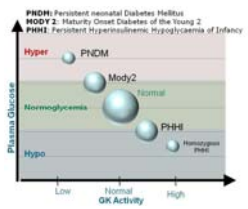
Presenter Disclosure Information

The American Diabetes Association requires the following disclosure to the participants:

Carmen Valcarce, PhD

Employee of TransTech Pharma, LLC

GK is the Physiological Glucose-sensor:
Genetic Target Validation in Humans



- In humans, abnormal GK activity due to activating or inactivating mutations is linked to hyperglycemic and hypoglycemic conditions respectively

- In humans, loss of function mutations on the GKRP are associated with increased plasma lipids (Rees et al. J Clin Invest. (2012) 122: 205-217)
- In rodents, GKRP KO mice showed:
  - Decrease of GK expression in the liver
  - Glucose intolerance
  - Insulin resistance

A Successful Approach to GK Activation

- Liver selective compounds that do not activate GK in the beta-cells
- Compounds that do not affect the inhibition of GK by GKRP in the liver

Two essential criteria, validated by human mutations, to sustain glucose control without causing hypoglycemia or hyperlipidemia

Key Differentiators of TTP399

	TTP399	Dual Acting GKAs	Other Hepatoselective GKAs
Activation of GK in β-cells	No	Yes	No
Activation of GK in the liver	Yes	Yes	Yes
Affect GK / GKRP interaction	No	Yes	Yes
Stimulation of insulin secretion independent of glucose	No	Yes	No
Hypoglycemia	**No**	**Yes**	**No**
Increase lipids	**No**	**Yes**	**Yes**
Liver toxicity	**No**	**Yes**	**Yes**
Lack sustained efficacy	*No (tbd)*	**Yes**	N/A

Data Summary from Animal Studies using TTP's Liver-selecive GKAs

Efficacy

- **Normalization of 24h blood glucose** in mild and severe diabetic animal models
- **Significant reduction in HbA_{1c}** in severe diabetic animal models (ob/ob mice)
- **Normalization of HbA_{1c} in mild diabetic animals** (GK rats)
- Effective in Type 1 Diabetic animal models (BB rats and Type 1 minipigs)
- Additive/synergistic effects when in combination with other antidiabetic agents (Met, DPPIV, GLP1 agonist)
- Potential improvement in plasma and liver lipids
- Weight reduction
- Increase in GLP-1 secretion

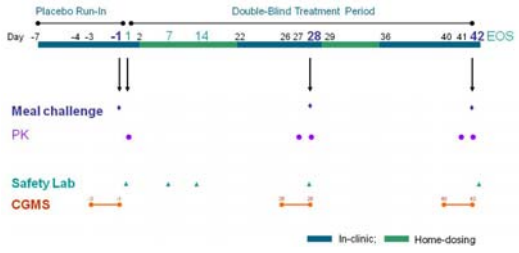
Safety

- **No hypoglycemia related to the treatment** in fed or fasted, diabetic or normal animals
- **Non-detrimental effects in plasma or liver lipids**
- **Well tolerated (No liver tox)**
- **No signs of tachyphylaxis**
- No changes in food intake
- No accumulation of lactate in plasma or liver
- No rebound when treatment was discontinued
- No genotx or reprotox findings

TTP399-201

- A double-blind, 6-week multiple-dose study in T2DM patients on stable doses of Metformin
- Phase 1b/2a
- Study drugs/Treatments
  - 400 mg BID, 800 mg QD, 800 mg BID and placebo
- Objectives:
  - To assess the safety and tolerability of TTP399
  - To evaluate the pharmacodynamic (PD) effect
  - To investigate the pharmacokinetic (PK) characteristics

Study Diagram



Baseline Characteristics

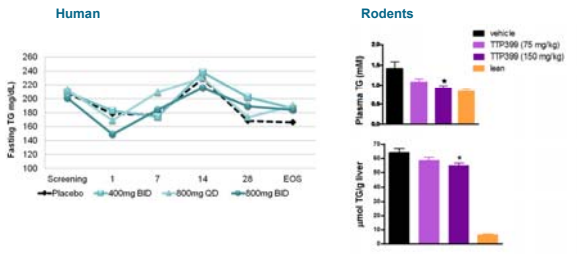
	400-mg BID (n=29)	800-mg QD (n=31)	800-mg BID (n=30)	Placebo (n=30)	All (n=120)
Age	57.8 ± 8.7	55.2 ± 7.5	57.1 ± 8.0	57.5 ± 7.2	56.9 ± 7.8
Gender	14 F, 15 M	14 F, 17 M	11 F, 19 M	7 F, 23 M	46 F, 74 M
Weight (kg)	85.5 ± 13.1	90.3 ± 12.9	84.4 ± 18.6	96.6 ± 16.6	89.2 ± 16.1
BMI	30.5 ± 4.6	31.7 ± 3.9	30.4 ± 4.8	32.6 ± 3.6	31.3 ± 4.3
HbA_{1c} (%)	8.22 ± 0.89	8.23 ± 1.01	8.36 ± 0.92	8.04 ± 0.77	8.21 ± 0.90
Diabetic Hx (years)	7.7 ± 4.2	7.5 ± 3.7	11.2±8.3	8.4 ± 5.7	8.7 ± 5.9
Metformin dose (mg/day)	1565.5 ± 431.2	1541.9 ± 538.2	1558.3 ± 501.4	1686.7 ± 418.3	1587.9 ± 473.3

mean ± SD

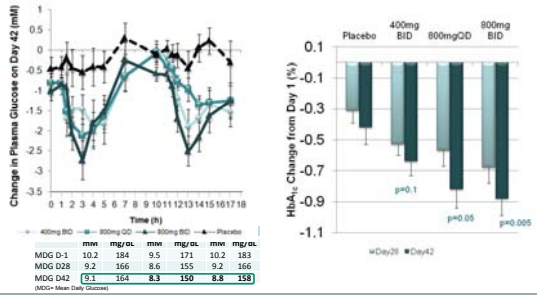
TTP399-201 TEAE

	400-mg BID (29)	800-mg QD (31)	800-mg BID (30)	Placebo (30)
Subjects with at least one TEAE	17	13	19	12
Headache	3	4	4	4
Dizziness	2	2	1	2
Diarrhea	2	2	1	1
Symptomatic Hypoglycemia	**0**	**0**	**0**	**1**
Elevated LFTs	**0**	**0**	**0**	**0**

In Contrast to Other GKAs, TTP399 does not Affect Fasting Plasma Lipids



TTP399 Significantly Improved Plasma Glucose and HbA_{1c} in Type 2 Diabetic Subjects on Stable Doses of Metformin after only 6 weeks of Treatment



	mM	mg/dL	mM	mg/dL	mM	mg/dL
MDG D-1	10.2	184	9.5	171	10.2	183
MDG D28	9.2	166	8.6	155	9.2	166
MDG D42	9.1	164	8.3	150	8.8	158

(MDG= Mean Daily Glucose)

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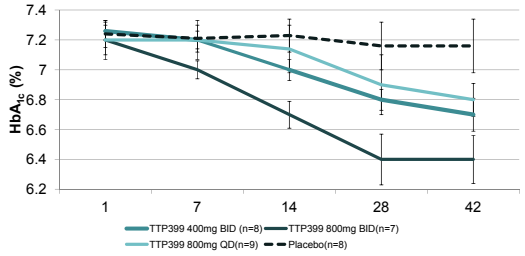
TTP399 Normalized Glycemic Control even in Subjects "Well-controlled" on Metformin (HbA_{1c} ≤7.5 %at BL) without Inducing Hypoglycemia



None of the Placebo-treated subjects reached HbA_{1c}≤6.5%

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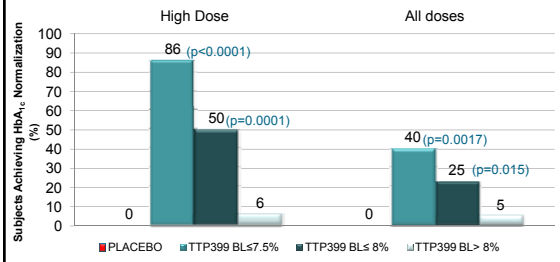
% of Subjects Achieving HbA_{1c} Normalization (≤6.5%) after 6-weeks of Treatment with TTP399



None of the Placebo-treated subjects reached HbA1c≤6.5%

TTP399 Conclusions

- TTP399 is safe and well tolerated
- The clinical results obtained to date are completely consistent with preclinical data and the MOA of liver selective GKAs:
  - Normalization of HbA_{1c} without induction of hypoglycemia
    - **Suitable for intensive glucose control therapy**
  - No stimulation of glucose independent insulin secretion in healthy volunteers or type 2 diabetic patients
  - No hypoglycemia at any dose tested
  - Treatment effect on both postprandial glucose and fasting glucose
  - No increase in fasting plasma lipids
  - No increases in plasma lactate

Acknowledgements

- GKA Discovery Teams at Novo Nordisk and TransTech Pharma
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Thank you for your Attention