Horizon Scanning

TechScan

Report No. : 003/2021

TTP399 As An Adjunct Therapy For Type 1 Diabetes Mellitus

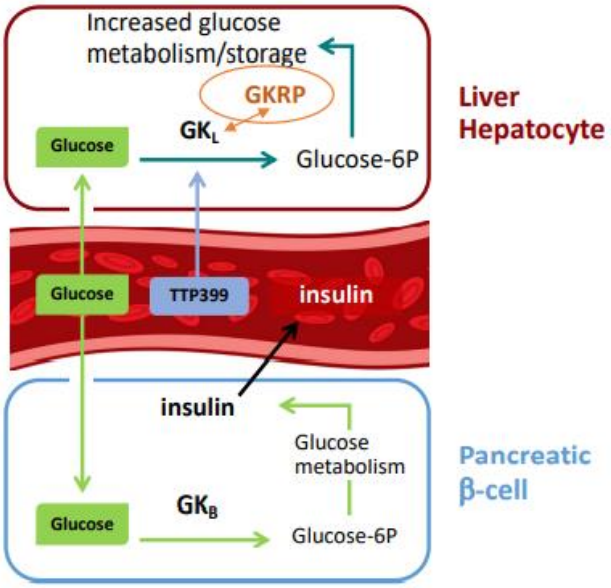
Keywords: glucokinase activator, hepatic-selective, anti-diabetic drug

SUMMARY OF TECHNOLOGY

TTP399 is an investigational oral medication being developed as an adjunct therapy to insulin indicated for better glycaemic control for patients with type 1 diabetes mellitus. The studied dosing is 800mg daily.[1]

It is first-in-class, liver-selective glucokinase (GK) activator which offers new pathway of anti-diabetics medication via the mechanism of glucokinase activation.

Figure 1 Mechanism of action of TTP399



TTP399 acts on liver glucokinase which converts glucose to glucose-6-phosphate and subsequently stored as glycogen, subsequently lead to improved clearance of glucose from the blood stream. TTP399 does not activate GK of pancretic β-cells and does not disrupt the interaction between GK and GKRP (GK Regulatory Protein) thus keeping physiological control of GK.

In glucose homeostasis in the body, glucokinase (GK) is a regulator of glucose homeostasis and acts as the physiological glucose sensor which responsible for increased glucose metabolism and its storage. GK has two main distinctive

characteristics that make it a good choice for blood glucose control. First, its expression is mostly limited to tissues that require glucose-sensing (mainly liver and pancreatic β-cells). Second, GK is able to sense changes in serum glucose levels and modulate changes in liver glucose metabolism that in turn regulate the balance between hepatic glucose production (HGP) and glucose consumption, and to modulate changes in insulin secretion by the beta-cells. The concept of GK activation for the treatment of diabetes is proven to be effective and safe in normalizing glycemia in animal models of type 1 and type 2 diabetes by a mechanism entirely distinct from the action of antidiabetic therapies currently on the market.[1]

TTP399 has not yet received any approval from any regulotary bodies. TTP399 also completed a 6 month phase 2 trial in patients with type 2 diabetes where it achieved statistically significant reductions in HbA1c with negligible incidences of hypoglycemia and hyperlipidemia.[2]

INNOVATIVENESS

Novel, completely new	√
Incremental improvement of the existing technology	
New indication of an existing technology	

DISEASE BURDEN

Type 1 diabetes mellitus (T1DM) also known as autoimmune diabetes, is a chronic disease characterized by insulin deficiency due to pancreatic β-cell loss and leads to hyperglycaemia.[3, 4]

The incidence of T1DM is very low in Asia, which is approximately 2 to 5 per 100,000 person-years. From 2009 to end of 2012, there were a total of 657,839 patients enrolled in the National Diabetic registry. Nearly all the patients enrolled, 653,326, were diagnosed with Type 2 Diabetes Mellitus (T2DM). As of end 2012, patients diagnosed with Type 1 Diabetes Mellitus comprised only 0.6%.[5]

People with T1DM require life-long insulin replacement therapy. Without insulin, diabetic ketoacidosis (DKA) develops and is life-threatening.[6] Intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in patients with T1DM by a range of 39% to 76%.[4]

Studies have shown that good glycaemic control in early part of the disease results in lower frequency of chronic diabetes complications[4] as mentioned above. However, according to data in T1DM Exchange registry in United State, only a minority of adults and youth with T1DM in the United States achieve goals for HbA1c. Mean HbA1c in 2016–2018 increased from 65 mmol/mol at the age of 5 years to 78 mmol/mol between ages 15 and 18, with a decrease to 64 mmol/mol by age 28 and 58–63 mmol/mol beyond age 30. The American Diabetes Association (ADA) HbA1c goal of <58 mmol/mol for youth was achieved by only 17% and the goal of <53 mmol/mol for adults by only 21%. Noticeably, insulin pump use also increased from 57% in 2010–2012 to 63% in 2016–2018. Continuous glucose monitoring (CGM) increased

from 7% in 2010–2012 to 30% in 2016–2018, rising >10-fold in children <12 years old. HbA1c levels were lower in CGM users than nonusers. Severe hypoglycemia was still a problem and most frequent in participants ≥50 years old and diabetic ketoacidosis was most common in adolescents and young adults.[7]

CURRENT OPTIONS FOR PATIENTS

According to Malaysian Clinical Practice Guidelines (CPG) for management of type 1 diabetes mellitus in children & adolescents, the treatment targets are aiming towards:[4]

- achievement of the ideal blood glucose level (near physiological glucose control)
- no significant hypoglycaemia or recurrent diabetic ketoacidosis (DKA) through self-monitoring of blood glucose (SMBG) and optimal HbA1c level
- absence of hypoglycaemia unawareness
- normal growth and development
- normal psychosocial development and adjustment in dealing with a chronic disease
- prevention of long-term diabetic complications

Insulin treatment must be started as soon as possible after diagnosis in all children with hyperglycaemia to prevent metabolic decompensation and diabetic ketoacidosis. Nevertheless, insulin is only part of a comprehensive diabetes management including nutritional management, physical activity, education, rules for sick days, surgery, and psychosocial support.[8]

Insulin requirement differs depend on which phase the patient in and the age of the patient. During the partial remission phase, the total daily insulin dose is often less than 0.5 IU/kg/day. Outside the partial remission phase, insulin requirement for prepubertal children is within 0.7-1.0 IU/kg/day and during pubertal age the requirements may rise substantially above 1 and even up to 2 U/kg/day.[4, 8]

Children on twice daily regimens often require about two thirds of their total daily dose (TDD) in the morning and about one third in the evening. About one third of each insulin dose is rapid- or short-acting insulin and about two thirds is intermediate-acting insulin. Children on basal-bolus regimens require night-time intermediate-acting insulin between 30% (if on regular insulin) and 50% (if on rapid-acting insulin) of TDD. About 50% as rapid-acting or about 70% as regular insulin is divided up between three and four pre-meal boluses.[4]

As mentioned in previous section, obtaining good glycaemic control is still underway therefore efforts are tremendously made to achieve that aim and eventually reduce the risk of developing possible complications.

POTENTIAL IMPACT OF TECHNOLOGY

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on (i) effectiveness of TTP399 (ii) safety of TTP399.

There was one retrievable unpublished scientific evidences on the effectiveness and safety of TTP399 for Type 1 Diabetes Mellitus.

SimpliciT1 (NCT03335371)[9] is a randomised, double-blind, placebo-controlled phase 1b/2 adaptive study of TTP399. Eligible participants were adults diagnosed with type 1 diabetes before age 40 years and at least one year prior to screening with a hemoglobin A1c (HbA1C) 7.5-9.0% (53-80 mmol/mol). Phase 2 activities were conducted in two parts. Part 1 (learning phase) randomly assigned 20 participants using continuous glucose monitors and continuous subcutaneous insulin infusion (CSII). Part 2 (confirming phase) randomly assigned 85 participants receiving multiple daily injections of insulin or CSII. In both parts 1 and 2, participants were randomly assigned to 800 mg TTP399 daily dosing or matched placebo (fully blinded) and treated for 12 weeks. The primary end point was change in HbA1c from baseline to week 12.[10]

Table 1 Baseline characteristic of participants in the study.

	Learning Phase		Confirming Phase	
	Placebo (n= 11)	TTP399 (n=8)	Placebo (n= 43)	TTP399 (n=38)
Sex, female	8 (73%)	5 (63%)	24 (56%)	14 (37%)
Age (years)	47 (10)	38 (15)	42 (13)	43 (15)
Race				
White	11 (100%)	7 (87%)	41 (95%)	36 (95%)
Black or African American	0	1 (13%)	1 (2%)	0
Asian	0	0	1 (2%)	2 (5%)
Ethnicity -not Hispanic or Latino	11(100%)	8 (100%)	41 (95%)	37 (97%)
Weight (kg)	82·8 (15·1)	80·2 (14·3)	83·6 (15·0)	83·1 (18·4)
BMI (kg/m²)	29·0 (4·1)	28·4 (3·3)	28·3 (3·8)	27·6 (4·0)
Age at type 1 diabetes diagnosis	18 (11)	9 (7)	16 (10)	16 (9)
Duration of diabetes (years)	29 (17)	29 (16)	26 (14)	26 (13)
Insulin pump users	11 (100%)	8 (100%)	27 (63%)	20 (53%)
CGM User	11 (100%)	8 (100%)	25 (58%)	24 (63%)
HbA_{1c} Baseline				
%	7·4 (0·4)	7·2 (0·4)	7·5 (0·60)	7·6 (0·6)
mmol/mol	58 (4·5)	57 (4·7)	61 (6·5)	62 (5·8)
β-hydroxybutyrate (mmol/L)	0·19 (0·32)	0·12 (0·21)	0·14 (0·25)	0·11 (0·12)
C-peptide				
Undetectable (<0·004 ng/mL)	5 (45%)	5 (63%)	22 (51%)	20 (53%)
Daily Insulin dose (IU/kg)				
Total (IU/kg)	0·59 (0·14)	0·65 (0·11)	0·65 (0·20)	0·68 (0·27)
Basal (IU/kg)	0·31 (0·07)	0·38 (0·06)	0·30 (0·12)	0·32 (0·17)
Bolus (IU/kg)	0·28 (0·10)	0·27 (0·13)	0·35 (0·13)	0·37 (0·15)

Efficacy

There was statistically significant improvement in glycaemic control as shown in Table 3. The change in HbA1c from baseline to week 12 between TTP399 and placebo was −0.7% (95% CI: −1.3, −0.07) p=0.032 in part 1 and −0.21 (95% CI: −0.39, −0.04) p=0018 in part 2. Subgroup analysis has shown that TTP399 significantly reduced HbA1c compared to placebo in patients that decreased their

insulin dose or maintained stable insulin dose throughout the study. Significantly fewer patients in the TTP399-treated group needed to increase their insulin dose to maintain their glycemic targets.[10]

Table 2 Change in HbA1c between TTP399 and placebo group.

	Learning Phase			Confirming phase		
	Placebo (n= 11)	TTP399 (n=8)		Placebo (n= 43)	TTP399 (n=38)	
HbA1c %						
Baseline (SD)	7·4 (0·4)	7·2 (0·4)		7·5 (0·60)	7·6 (0·6)	
Week 12 change from baseline (SE)	0·08 (0·20)	-0·60 (0·20)		0·07 (0·06)	-0.14 (0.06)	
Treatment effect (%) (CI, p)	NA	-0.69 (-1.30, -0.07)	p=0.032	NA	-0·21 (-0.39, -0.04)	p=0.018
Treatment effect (mmol/mol)		-7.5			-2.3	
Treatment effect (%) (CI, p) (Product estimand)*				NA	-0·31 (-0.5, -0.12)	p=0.0017
Treatment effect (mmol/mol) (Product estimand)*					-3.3	
Responders**						
Proportion with composite response	0	5 (62%)		5 (12%)	16 (42%)	
Treatment effect (odds ratio)	NA		p=0.005	NA	9.6 (2.5, 36.7)	p=0.001
Daytime % Time in Target Range						
Baseline	65% (13)	70% (9)		57% (11)	51% (14)	
Week 12 change from baseline	-9.2 (2.5)	2.6 (3.4)		-7.8 (2.3)	0.1 (2.6)	
Treatment effect (%)	NA	11.8 (2.58, 20.95)	p=0.016	NA	7.8 (0.93, 14.68)	p=0.027

Safety

The incidence of treatment-emergent adverse events (AEs) was similar between the intervention group and placebo group[10] as shown in Table 1.

Table 3: Incidence of Adverse Events in Simplici-T1 Study.

	Learning Phase		Confirming Phase	
	Placebo (n=11)	TTP399 (n=9)	Placebo (n=45)	TTP399 (n=40)
Number of AEs reported	16	13	83	58
Participants with at least one AE	8 (73%)	6 (67%)	29 (64%)	26 (65%)
Participants with at least 1 drug-related AE	2 (18%)	1 (11%)	3 (7%)	2 (5%)
Participants with AE leading to death	0	0	0	0
Participants with AE leading to discontinuation	0	0	0	0
Number of SAEs	0	0	1	1
Participants with at least 1 SAE related to drug	0	0	0	0
Participants with at least 1 SAE	0	0	1 (2%)	1 (2%)
Coronary Artery Disease	0	0	1 (2%)	0
Non-Cardiac Chest Pain	0	0	0	1 (2%)

TTP399 did not alter liver function or increase plasma triglycerides. Despite a greater decrease in HbA1c with TTP399, the frequency of severe or symptomatic hypoglycemia decreased by 40% relative to placebo in part 2 (confirming phase) as shown in Table 4. In both parts 1 and 2, plasma β-hydroxybutrate and urinary ketones were lower during treatment with TTP399 than placebo.[10]

Table 4 Incidence of hypoglycaemia between TTP399 group versus placebo.

	Placebo (n=45)	TTP399 (n=40)
Number of participants with hypoglycemic AEs	**9 (20%)**	**5 (12%)**
Total number of hypoglycemic AEs	27	12
Severe hypoglycemia	1	0
Symptomatic hypoglycemia	26	12
Events per person-exposure month	0.2	0.1
Week 2 visit to end of the study		
Number of participants with hypoglycemic AEs	**8 (18%)**	**2 (5%)**
Events per person-exposure month	0.15	0.04

Cost

There was no retrievable evidence on cost-effectiveness study on this medication. Otherwise, there was no governmental or societal issues noted.

In conclusion, TTP399 along with prescription of insulin has the potential to improve glycaemic control with reduced incidence of hypoglycaemia among Type 1 diabetic patients. However, larger studies are needed to prove that claim.

EVIDENCE

Klein KR, Freeman JLR, Dunn I, et al. The SimpliciT1 Study: A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Adaptive Study of TTP399, a Hepatoselective Glucokinase Activator, for Adjunctive Treatment of Type 1 Diabetes. Diabetes Care. 2021:dc202684.

REFERENCES

1. VTV Therapeutics. TTP399. 2020. Available from: https://vtvtherapeutics.com/pipeline/ttp399/. Accessed on 24 December 2020.
2. Egan A, Vella A. TTP399: an investigational liver-selective glucokinase (GK) activator as a potential treatment for type 2 diabetes. Expert Opin Investig Drugs. 2019;28(9):741-747.
3. Katsarou A, Gudbjörnsdottir S, Rawshani A, et al. Type 1 diabetes mellitus. Nature Reviews Disease Primers. 2017;3(1):17016.
4. Ministry Of Health Malaysia. Management of Type 1 Diabetes Mellitus In Children & Adolescents. 2015. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/CPG/Endocrine/2a.pdf. Accessed on 6 January 2021.

5. Ministry Of Health Malaysia. National Diabetes Registry Report 2009 - 2012. 2013. Available from: https://www.moh.gov.my/moh/resources/Penerbitan/Rujukan/NCD/Diabetes/National_Diabetes_Registry_Report_Vol_1_2009_2012.pdf. Accessed on 5 Januari 2020.

6. Lucier J, Weinstock RS. Diabetes Mellitus Type 1: StatPearls Publishing, Treasure Island (FL); 2020 2020.

7. Foster NC, Beck RW, Miller KM, et al. State of Type 1 Diabetes Management and Outcomes from the T1D Exchange in 2016-2018. Diabetes technology & therapeutics. 2019;21(2):66-72.

8. International Society for Pediatric and Adolecent Diabetes (ISPAD). ISPAD Clinical Practice Consensus Guidelines 2018: Insulin Treatment In Children And Adolescents With Diabetes. 2018. Available from: https://cdn.ymaws.com/www.ispad.org/resource/resmgr/consensus_guidelines_2018_/9.insulin_treatment_in_child.pdf. Accessed on 10 March 2021.

9. Klein KR, Freeman JLR, Dunn I, et al. The SimpliciT1 Study: A Randomized, Double-Blind, Placebo-Controlled Phase 1b/2 Adaptive Study of TTP399, a Hepatoselective Glucokinase Activator, for Adjunctive Treatment of Type 1 Diabetes. Diabetes Care. 2021:dc202684.

10. Valcarce C, Freeman JL, Dunn I, et al. The Simplici-T1 trial: Activation of glucokinase by TTP399 improves glycemic control in patients with T1DM 2020. Available from: https://vtvtherapeutics.com/wp-content/uploads/2020/09/EASD2020_presentation-50-_FINAL.pdf. Accessed on 20 February 2021.

Disclosure: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Horizon Scanning UNIT,
MaHTAS, Ministry of Health, Malaysia,
Email: htamalaysia@moh.gov.my
Web: http://www.moh.gov.my