MSTM 101

MSTM-101: A NOVEL SALT OF METFORMIN EICOSAPENTAENOIC PANTOTHENATE FOR THE TREATMENT OF DIABETES

- A Novel Next Generation Metformin
- An Important Contribution To Diabetes Therapy Offering Physicians The Prospect of a New, First-Line, Oral Treatment for Diabetic Patients With the Potential to Regulate Blood Glucose and Slow the Incidence of Cardiovascular Events
- Designed for Simple Dissociation of Salt in the Physiological Fluid to Release Metformin and EPA-PA
- All The Released Actives Metformin, Eicosapentaenoic Acid and Pantothenic Acid are Expected to have Beneficial Pharmacological Effects
- Expected to be More Therapeutically Synergistic in Controlling Glycemia and Elevated Triglyceride Levels than the Current Standard of Care
- Preclinical Work Nearing Completion; Ready For GLP Tox And Clinical Development
- US Patent : US 8952068 B2 / Filed with 10 National Patent Offices

1. Opportunity overview

MSTM-101 is a differentiated drug candidate for the treatment of type 2 diabetes mellitus. The drug is a potential "next-generation metformin" that could regulate hyperglycemia and dyslipidemia. MSTM-101 is expected to have a significantly improved activity in the treatment of diabetes due to the expected pharmacologic effect from the omega 3 fatty acids and pantothenic acid to control triglycerides and other lipid metabolism.

MSTM-101 is a novel molecular salt of metformin with conjugate of Eicosapentaenoic acid (EPA)-D Pantothenate. Metformin is linked with EPA -pantothenic acid conjugate with through simple ionic bond, which undergoes dissociation in the physiologic medium to release metformin active moiety. EPA-D Pantothenate undergoes hydrolytic cleavage by the enzymes present in the system. The presence of hydrolytic bond in the molecule control the release of EPA and PA and possibly result in the effective delivery of the active moieties.

We have completed Biopharmaceutical assessment (solubility in water) and pharmacokinetic study in the rats. Follow on pharmacokinetic and efficacy studies in animal models are ongoing/ being planned. The company believes that MSTM-101 is an attractive differentiated candidate for the treatment of diabetes. Our studies indicate that MSTM-101 should achieve a favorable target product profile as described below:

- Oral route of administration with various formulations options
- Potential disease modification due to synergistic pharmacology with omega 3 fatty acid/pantothenic acid.
- Expected to be offer beneficial pharmacological effects (glycemic and lipid control) than the current therapy for diabetes

2. Market description

Type 2 diabetes mellitus is the most common form of diabetes characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.

Type 2 diabetes is on the rise worldwide. The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014. The World Health Organization (WHO) estimates that 90 percent of people around the world who suffer from diabetes suffer from type 2 diabetes (WHO report). Diabetes is considered to be a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation. WHO projects that diabetes will be the 7th leading cause of death in 2030. The International Diabetes Federation (IDF) reports that as of 2013 there were more than 387 million people living with diabetes. 29.1 million people in the United States have diabetes.

In diabetes mellitus, dyslipidemia is one of the key risk factors for cardiovascular disease (CVD). The different components of diabetic dyslipidemia are not isolated abnormalities but closely linked to each other metabolically. The underlying disturbances are considered to be hepatic overproduction and delayed clearance of TRLs. Recent results have unequivocally shown that triglyceride-rich lipoproteins and their remnants are atherogenic. Studies also have consistently reported that high prevalence (about 35 to 50%) of dyslipidemia in T2D subjects treated with statins leaving the subjects at high residual risk (Taskinen M.R et al., 2015).

“The American Heart Association” considers diabetes to be one of the seven major risk factors for cardiovascular disease. The statistics published by The American Heart Association suggests that there is a strong correlation between cardiovascular disease (CVD) and diabetes. a) at least 68 percent of people age 65 or older with diabetes die from some form of heart disease. b) adults with diabetes are two to four times more likely to have heart disease than adults without diabetes. This triad of poor lipid counts (high TG, LDL and low HDL) often occurs in patients with premature coronary heart disease. It is characteristic of a lipid disorder associated with insulin resistance called atherogenic dyslipidemia, or diabetic dyslipidemia in those patients with diabetes (The American Heart Association).

- Recent data indicate that diabetes *per se* increases CVD risk about two-fold on average but the risk varies widely depending on the population. Importantly, those with diabetes and coronary heart disease are at substantially higher risk of future CVD events (Taskinen M.R et al., 2015)

- CVD Death Rates: In 2003–2006, after adjusting for population age differences, cardiovascular disease death rates were about 1.7 times higher among adults aged 18 years or older with diagnosed diabetes than among adults without diagnosed diabetes.

  (http://www.diabetes.org/diabetes-basics/statistics/).

3. Unmet medical need

Dyslipidemia is one of the key risk factors for cardiovascular disease (CVD) in diabetes mellitus; are generally caused by increased free fatty acid flux secondary to insulin resistance and aggravated by increased inflammatory adipokines. The overall cardiometabolic risk is driven by a complex interplay between many factors such as hyperglycemia, and the components of the metabolic syndrome commonly associated with type 2 diabetes. A major cause is considered to be the atherogenic dyslipidemia, which consists of elevated plasma concentrations of both fasting and postprandial triglyceride-rich lipoproteins (TRLs), small dense low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) cholesterol (Taskinen M.R et al., 2015).

Despite the advances made in the prevention and management of cardiovascular disease, people with diabetes mellitus continue to have alarmingly high morbidity and mortality secondary to cardiovascular disease. Diabetes-related changes in plasma lipid levels or the spectrum of dyslipidemia in diabetes mellitus and, which is attributed mostly to insulin resistance and insulin deficiency (Mooradian AD et al., 2009).

Importantly, current standard of care including statins fail to adequately correct these features of dyslipidemia and several recent trials have failed to show benefits from fibrates or niacin when added to statins (Taskinen M.R et al., 2015).

4. MSTM-101: Scientific Rationale

Metformin remains the drug of choice as first-line therapy in Type 2 diabetes. Metformin is one of only two oral anti-diabetics in the World Health Organization Model List of Essential Medicines (Most efficacious, safe and cost effective). Scientific literature signify the treatment

with metformin is associated with a decreased risk of cardiovascular mortality and indicate its moderate cardio-protective effects. Interestingly, metformin also exerts its beneficial effect on the blood lipid profile, which is characterized by a significant reduction in circulating triglycerides (TGs) and VLDL cholesterol and increased HDL cholesterol levels. This could be involved in its cardioprotective effect observed in obese patients, although the exact molecular mechanism(s) of action of metformin still remains incompletely understood. Preclinical studies have suggested that metformin exerts a beneficial effect on circulating lipids by lowering plasma TG, through a selective BAT-mediated increase in VLDL-TG uptake/lipolysis or activation of hepatic AMP-activated protein kinase (AMPK) (Geerling J.J et al. 2014

EPA is an omega-3 fatty acid and is a GRAS molecule with well known clinical safety data in humans. Omega-3 fatty acids and esters of eicosapentaenoic acid are approved as drug for severe hypertriglyceridemia by USFDA. Several multi-center clinical trials have demonstrated the Clinical Efficacy and Safety of eicosapentaenoic acid for the treatment of lipid disorders, more specifically hypertriglyceridemia. Literature also suggests a possible protective agent against risk factors of cardiovascular disease and indicate cardio protective actions of eicosapentaenoic acid

- Data from the clinical studies indicates that Vascepa® (Icosapent Ethyl or ethyl ester of eicosapentaenoic acid) treatment resulted in Significant Reductions in Potentially Atherogenic Lipid Parameters in Statin-Treated Patients With Type 2 Diabetes and Persistent High Triglycerides (reduced the median concentrations of VLDL and LDL particles in patients with Type 2 diabetes who, despite statin therapy, have persistent high TG levels (≥200 and <500 mg/Dl). In addition apolipoprotein B (Apo B), which is carried on VLDL and LDL, was also significantly reduced by 9.3% compared with placebo.

- The ongoing study for Vascepa (a trial known as REDUCE-IT), the first multinational cardiovascular outcomes study evaluating the benefit of pure EPA therapy, or any triglyceride lowering therapy, as an add-on to statins in patients with high cardiovascular risk despite having stable statin therapy, with elevated triglyceride levels (≥200 and <500mg/dL) will provide more insights.

D-Pantothenic acid, is a GRAS listed water soluble vitamin is reported to be involved in the synthesis of Pantethine and increase the CoA levels within the cells, which favorably modifies lipoprotein metabolism. Pantethine in conjunction with the intermediary cysteamine, inhibits acetyl-coenzyme (CoA) carboxylase and 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase, thereby affecting TG synthesis and lipoprotein metabolism. However, the full mechanism of action in lowering cholesterol levels is not fully understood (Kelly G.S., 2011 and Evans M et al., 2014).

Cellix believes that MSTM-101 would be an attractive differentiated candidate for the treatment of diabetes and will have a unique profile of controlling hyperglycemia and lipid abnormalities thereby reducing atherogenic lipid parameters, from a single drug. It will also improve the patient compliance by convenient delivery of metformin and eicosapentaenoic acid.

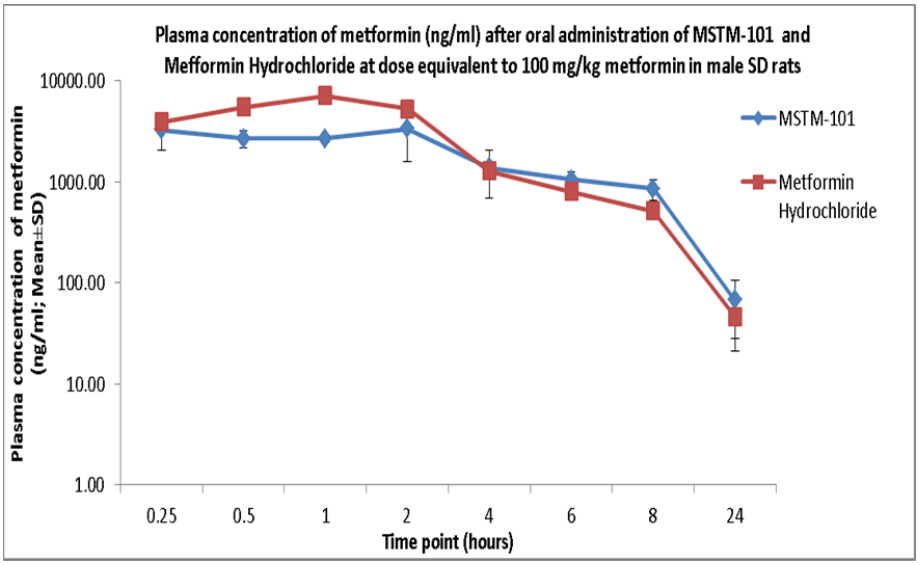
5. Summary of Pre-clinical data

We have completed preliminary solubility assessment in water and pharmacokinetics of MSTM-101 in rats.

- The solubility of the compound has suggested that it is quite acceptable for developing various oral dosage forms that could ensure optimal delivery of all the bio-actives in the treatment of diabetes and associated dyslipidemia. The release of the actives is shown to be mediated by simple dissociation/ionization of the compound to release metformin and EPA-PA conjugate.

- A comparative *in vivo* rat oral pharmacokinetic study was conducted at a dose equivalent to 100 mg/kg of metformin (in comparison to metformin hydrochloride). The systemic exposure to metformin was comparable to that of metformin hydrochloride; and marginal reduction in C_{max}. In addition, the preliminary data indicates that systemic exposure to free fatty acid (EPA) was higher than that of the reference control animals (back ground levels of plasma free EPA).

PK Parameters	MSTM-101 (dose equivalent to 100 mg/kg metformin)	Metformin.Hcl (dose equivalent to 100 mg/kg metformin)
Cmax(ng/ml)	4412.1 ± 1062.1	7191.3 ± 784.7
Tmax(h)	1.1 ± 1.0	1.0 ± 0.0
AUC(0-t) (hr*ng/ml)	**19176.3 ± 4294.0**	**23090.6 ± 2225.3**
Half life (hr)	4.6 ± 1.0	4.3 ± 0.9



EPA from MSTM-101		
	Mean	**SD**
Cmax (ng/ml)	58807.11	31710.7
$AUC_{(0-t)}$ (hr*ng/ml)	205954.29	68032.7
Tmax (h)	1.75	1.5

PA from MSTM-101		
	Mean	**SD**
Cmax (ng/ml)	5560.78	2583.4
$AUC_{(0-t)}$ (hr*ng/ml)	37691.17	16034.6
Tmax (h)	2.38	3.8

Note: Free EPA and Pantothenic acid in the plasma samples of control animals were <LLOQ (back ground levels)

6. References

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