MLR-1023: A First-in-Class, Clinical Stage Candidate for Type II diabetes

» “Next generation” insulin sensitizer that does not have PPAR activity

» Orally bioavailable small molecule

» Weight neutral

» β-cell function preservation

» Repositioned drug candidate with demonstrated safety through Phase II clinical trials

» Clinical evidence of blood glucose lowering

» US IND approved for clinical development

» Robust patent estate
OPPORTUNITY OVERVIEW
MLR-1023 is a Phase I clinical stage drug candidate for the treatment of type II diabetes with possible utility in other metabolic diseases. The drug is a potential “next-generation” insulin sensitizer that works independently of a PPAR mechanism. MLR-1023 improves glycemic control by directly and selectively activating the enzyme Lyn kinase. Lyn kinase has previously been shown to modulate the insulin-signaling pathway. Indeed, the extrapancratic glycemic control activity of glimepiride (Amaryl®) is mediated through a non-specific and indirect Lyn kinase activation. Therefore, MLR-1023 is the first described specific and direct activator of Lyn kinase that elicits glycemic control activity through potentiation of insulin activity.

MLR-1023 was formerly in development by Pfizer through Phase II clinical trials for an unrelated chronic indication, but clinical development was halted for lack of efficacy. The drug, however, was shown to be safe and well tolerated in several clinical trials. Post-hoc analysis of blood glucose in those trials provides an early, statistically significant, indication that the drug has therapeutic potential towards diabetes.

On the basis of efficacy shown in validated in vivo preclinical models and safety data from previous long term pre-clinical exposures and several clinical studies, the Company believes that MLR-1023 is an attractive clinical candidate for type II diabetes. These studies indicate that MLR-1023 should achieve a favorable target product profile as described below:

- Once daily, oral route of administration
- Gold standard glucose lowering when used as monotherapy
- Superior to sulfonylureas with no risk of hypoglycemia
- Superior to thiazolidinediones and sulfonylureas with neutral effect on weight
- Potential disease modification with β-cell sparing / improvement in β-cell function
- Broad combination use/products with metformin, thiazolidinediones, DPPIV inhibitors and sulfonylureas
- Favorable safety and tolerability profile (minimal to mild AEs at projected clinical dose. eg. headache)

Melior is now seeking a funding to advance the product through Phase II clinical trials in order to position it well for partnering with a multinational pharmaceutical company. The FDA has approved an Investigational New Drug (IND) application for the development of MLR-1023 for the treatment of type II diabetes.

MARKET DESCRIPTION
Type II Diabetes mellitus (DM) is a chronic, widespread condition whose etiology is not completely understood but which is characterized by defects in insulin secretion and insulin action. More than 230 million people worldwide are living with the disease, and this number is expected to rise to 350 million within 20 years. It is estimated that nearly 24 million Americans have DM, including an estimated 5.7 million who remain undiagnosed. At the same time, about 40 percent of those diagnosed are not achieving the blood-sugar-control target of HbA1c < 7% recommended by the American Diabetes Association. The HbA1c test measures average blood glucose levels over a two- to three-month period and elevated levels are associated with a significant increase in the risk of cardiovascular disease.
There is no cure for diabetes, but early stages of the disease may be managed with controlled diet and exercise. As the disease progresses blood glucose levels must be managed through an assortment of oral therapies including metformin, thiazolidinediones, sulfonylureas, DPP-4 inhibitors and others. Injectable approaches for the control of blood glucose include insulin, amylin and GLP-1 exercise. However, when diet and exercise fail, the typical first-line treatment is metformin, which is often supplemented with other drugs as the disease progresses. None of the existing therapies completely controls symptoms or disease progression and none are devoid of side effects.

Given the significant size of the patient population and the unmet medical need, the market potential for a novel diabetes therapy is considerable and should surpass $1 billion / year peak sales (worldwide). As a reference point, Januvia®, a moderately effective therapy that may be used in combination with metformin, achieved sales in excess of $1.75 billion in 2008. The drug received FDA approval in late 2006.

**MLR-1023 BACKGROUND**

MLR-1023 was originally developed by Pfizer as an anti-ulcer therapeutic and developed through Phase II clinical trials prior to discontinuation for lack of efficacy in this indication. In Phase II clinical trials, MLR-1023 was administered to 125 healthy volunteers and 62 patients with chronic symptomatic gastritis and/or duodenitis, rheumatoid arthritis, or benign gastric ulceration for a period of 6 weeks, during which the drug was well tolerated at 6 times the projected dose for use in type II diabetes.

Melior Discovery has acquired all rights to MLR-1023 as well as the original clinical dossier which was utilized in the preparation and filing of the new IND application for the treatment of type II diabetes.

**PRECLINICAL IN VIVO EFFICACY**

Melior Discovery identified MLR-1023 as an ideal repositioning candidate based on its structural qualities, human pharmacokinetic characteristics, clinical history, safety profile and patent status.

MLR-1023 was evaluated in a multi-therapeutic in vivo efficacy model panel (theraTRACE®) in order to detect unique, previously unidentified, therapeutic potential. In this evaluation, MLR-1023 elicited potent and robust prandial blood glucose lowering activity in an oral glucose tolerance test with an absence of effect on fasting glucose levels. In follow-on studies, MLR-1023 produced long-lasting regulation of blood glucose levels in multiple species in both pharmacologic and genetic models of type II diabetes.

**Acute Blood Glucose Lowering**

Single dose IP administration of MLR-1023 produced a dose-dependent decrease in blood glucose levels in an oral glucose tolerance test in normal mice (Figure 1). Further, MLR-1023 did not promote insulin secretion in cell-based studies and in vivo MLR-1023 did not increase plasma insulin levels nor reduce plasma glucose in fasted mice (data not shown). This is distinct from insulin and insulin level modulators (such as sulfonylureas) that produce hypoglycemia in normal fasted animals.

In comparison studies with metformin (Glucophage®), MLR-1023 produced equivalent efficacy, but was significantly more potent (Figure 1). In addition, in combination with metformin, MLR-1023 was able to considerably lower blood glucose below levels that could otherwise be achieved with optimum doses of metformin alone (data not shown).
**Figure 1.** Acute intraperitoneal administration of MLR-1023 produced a dose-dependent inhibition of blood glucose levels in an oral glucose tolerance test in mice. This blood glucose lowering was equivalent to that of metformin. (Animals fasted overnight prior to glucose challenge)

Oral administration of MLR-1023 also decreased blood glucose levels in Zucker fa/fa rats and normoglycemic rats subjected to oral glucose challenges (see Figure 2 below).

**Figure 2.** Acute oral administration of MLR-1023 to rats produced a dose dependent lowering of blood glucose levels following an oral challenge with glucose. (Animals fasted overnight prior to glucose challenge)
Chronic Blood Glucose Lowering

MLR-1023 also produced blood glucose-lowering responses in db/db mice (a genetic model with defective leptin receptors) that were equivalent to those of the PPARγ agonist rosiglitazone (Figure 3). However, the activities of MLR-1023 were differentiated from rosiglitazone in several important respects. First, as was demonstrated following acute administration experiments, the onset of MLR-1023’s glucose-lowering effects was significantly faster than the onset produced by rosiglitazone (3 days compared to 10 days). Second, MLR-1023 administration was completely devoid of weight gain compared to rosiglitazone; in separate experiments in diet-induced obese mice, MLR-1023 has demonstrated weight loss potential associated with reduction in fat pad mass. Third, db/db mice treated with MLR-1023 did not exhibit the extent of serum insulin lowering associated with pancreatic β-cell loss as mice treated with vehicle or rosiglitazone; this apparent preservation of β-cell function was borne out in histological studies showing that islets from mice chronically treated with MLR-1023 had increased insulin content and better preserved islet structure compared to untreated controls (Figure 4).

Another important feature of chronically administered MLR-1023 was the reduction in HbA1c levels in db/db mice. HbA1c levels, a critical parameter in human type II diabetes clinical studies, were reduced by more than 2.5% (Figure 5).

Figure 3. Chronic administration of MLR-1023 produced a long-lasting blood glucose lowering in db/db mice without accelerating weight gain.
**Figure 4.** MLR-1023 blocks beta cell degeneration in db/db mice. Eleven week-old mice were treated with either vehicle or MLR-1023 for 8 weeks. Photomicrographs below show insulin staining in β-cells.

**Figure 5.** MLR-1023 lowers HbA1c levels in db/db mice. Six week-old mice were treated with either vehicle or MLR-1023, at 3 different doses as indicated, for 8 weeks.
Combination Effects with Rosiglitazone
In combination with rosiglitazone, MLR-1023 attenuated the dramatic weight gain normally seen following administration of this agent (Figure 6). This suggests that in the clinic MLR-1023 could be utilized in combination with rosiglitazone to ameliorate this commonly reported side effect of rosiglitazone therapy.

Figure 6. MLR-1023 administered in combination with rosiglitazone inhibited rosiglitazone-mediated weight gain.

Activity in a Glucose Clamp
In ZDF rats subjected to a hyperinsulinemic euglycemic clamp procedure, MLR-1023 administration resulted in a significant increase in the glucose infusion rate required to maintain euglycemia. These results clearly indicate that MLR-1023 serves to potentiate insulin signaling.

Figure 7. MLR-1023 administered to ZDF rats increased glucose infusion rate in a hyperinsulinemic euglycemic clamp procedure. Eight week old Zucker fa/fa were administered MLR-1023 (100mg/kg po, qd) rosiglitazone (4mg/kg, po, qd) or vehicle for 7 days prior to clamp procedure. Insulin was infused at a constant rate of 20mU/kg/min.
MECHANISM OF ACTION
MLR-1023 is the first reported direct and specific activator of Lyn kinase. Activation of Lyn kinase has previously been shown to modulate IRS-1 and thereby increase glucose transport through the insulin receptor signaling pathway in adipose tissue, muscle, and liver (Figure 7, attached ref). Indeed, the extrapancreatic glycemic control activity of the insulin secretagogue glimepiride (Amaryl®) has been associated with that drug’s indirect and non-specific activation of Lyn kinase. To be clear, extensive in vivo pharmacology experiments establish that MLR-1023 potentiates insulin signaling as opposed to being an insulin mimetic.

MLR-1023 has been evaluated against a diverse set of targets and shown to be devoid of activities across a broad array of 7TMs, nuclear receptors and ion channel targets etc including established diabetes targets such as PPAR family members, DPP-IV, GLP-1 and others.

Mice deficient in lyn kinase (lyn knockout animals) did not respond to the blood glucose lowering activity of MLR-1023.

Figure 7. MLR-1023 signaling pathway

MLR-1023: A Type II Diabetes Clinical Stage Licensing Opportunity

CLINICAL EVIDENCE FOR MLR-1023 THERAPEUTIC ACTIVITY IN DIABETES

One of the Pfizer Phase II studies where MLR-1023 was evaluated for its effects in gastric ulcer patients provided Melior with partial blood glucose data that was gathered at baseline (pre-treatment) and during the clinical study. Evaluation of the available data revealed that MLR-1023 had a significant blood glucose lowering effect, as compared with placebo controls. Moreover, based upon baseline blood glucose levels, it appeared that 5 of the gastric ulcer patients studies were potentially diabetic; 4 of these were treated with MLR-1023 and 1 was treated with placebo. In “diabetics” MLR-1023 treatment appeared to result in a meaningful drop in blood glucose compared to placebo.

Figure 8. Change in blood glucose in a Phase 2 gastric ulcer study. Test article was administered for 6 weeks. Blood glucose at baseline and from one point in the study could be gathered from 17 MLR-1023-treated subjects and 11 placebo treat subjects. Five of the blood glucose reporting subjects were judged “diabetic” based upon baseline blood glucose. Four of these “diabetics” were treated with MLR-1023.
SAFETY & TOLERABILITY
All of the safety data that has been accumulated thus far (Table 1), strongly indicate that the compound, as well as activation of the molecular target, produce no apparent liabilities at multiples of the projected clinical dose.

In addition, Melior has consulted with Lyn kinase experts who have attested to the predicted safety of a compound that works by activating Lyn kinase. One of these experts has written a “white paper” providing the rationale for this predicted safety.

Finally, the lack of any long-term safety events with glimeipride (Amaryl®; a non-specific, indirect activator of Lyn kinase) further implicates the long-term safety of MLR-1023.

Adverse events (AEs) in clinical trials, up to 6 weeks in duration, were transient and mild to moderate in severity at doses that are 4-6 fold above anticipated effective clinical doses.

Table 1. Summary of safety and toxicology studies

<table>
<thead>
<tr>
<th>Species</th>
<th>Duration</th>
<th>Key Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>6-month feeding study</td>
<td>No hematology, clinical chemistry or histopathological changes at doses of up to 250 mg/kg/day</td>
</tr>
<tr>
<td>Monkey</td>
<td>3-month repeat-dose oral toxicity study</td>
<td>No hematology, clinical chemistry or histopathological changes at doses of up to 25 mg/kg bid</td>
</tr>
<tr>
<td>Human</td>
<td>6-week Phase IIa proof of concept study in gastric ulcer patients</td>
<td>No effects on hematology or clinical chemistry at doses of up to 100 mg tid</td>
</tr>
</tbody>
</table>

Note: Additional studies conducted included genotoxicity, Segment I and Segment II reproductive toxicology, safety pharmacology and hERG. No effects on blood pressure, heart rate, ECG were observed in dogs, telemetered monkeys or clinical studies at any dose evaluated.
MLR-1023: A Type II Diabetes Clinical Stage Licensing Opportunity

**ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION (ADME)**
MLR-1023 does not induce or inhibit cytochrome P450 and is not a substrate of major P450 isozymes. One major oxidized metabolite is created which may be formed by aldehyde oxidase. The metabolite is not a lyn kinase activator and is not active towards the glycemic control mechanism.

**CHEMISTRY AND MANUFACTURING CONTROLS (CMC)**
The major CMC attributes of MLR-1023 include:

- 3-step synthesis
- No significant issues regarding availability of raw materials
- API stable through 36 months

Melior has manufactured 11kg of API with reference standard and created enough drug product (powder in gelatin capsules) in various dosage forms (10mg, 25mg, 50mg, and 100mg) to supply studies through Phase IIa.

**INTELLECTUAL PROPERTY**
MLR-1023 is protected by a rigorous exclusivity mechanism, the foundation of which is provided by a method-of-use patent (claims allowed in US patent March, 2010). Importantly, in the context that no marketing approval has ever been granted for MLR-1023, method of use patent protection provides an effective solid barrier against entry for innovator and generic companies alike. This patent also has composition-of-matter claims for the combination of MLR-1023 with metformin.

In addition Melior has filed patents for the following inventions related to the MLR-1023 program:

- A method-of-use patent claiming MLR-1023 and a genus of compounds related to MLR-1023 for the treatment of type II diabetes and ancillary conditions
- A method to screen for lyn kinase activators in order to identify additional diabetes candidates
- Methods of activating IRS-1 and AKT
- A method-of-use patent claiming MLR-1023 and a genus of compounds related to MRL-1023 for the treatment of type I diabetes, based upon the β-cell preservation activity of MLR-1023.
- A method-of-use patent claiming MLR-1023 and a genus of compounds related to MLR-1023 for the treatment of lipodystrophy

A summary of the titles and filing dates for the patents filed related to the MLR-1023 program is listed in Table 2.

In addition, Melior has developed significant know-how as regards working with lyn kinase and screening for activators of this enzyme.
## Table 2. Patent Estate for MLR-1023

<table>
<thead>
<tr>
<th>Patent</th>
<th>Country</th>
<th>First Filing Date</th>
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<tbody>
<tr>
<td>Methods and Formulations For Treating Lipodystrophy</td>
<td>US provisional</td>
<td>July 2012</td>
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<tr>
<td>Methods for Treating Type I and Type II Diabetes Using Combinations With Insulin</td>
<td>PCT Application</td>
<td>December 2012</td>
</tr>
<tr>
<td>Prevention Of Pancreatic Beta Cell Degeneration</td>
<td>US</td>
<td>May 2010</td>
</tr>
<tr>
<td>Methods And Formulations For Modulating Lyn Kinase Activity, Treating Diabetes and Related Disorders</td>
<td>US, Europe, Japan, South Korea, Australia, India, Mexico, New Zealand, Hong Kong, Israel, Singapore, South Africa, Canada, China, Brazil</td>
<td>August 2005 (Issued)</td>
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<tr>
<td></td>
<td></td>
<td>August 2006 (Issued in South Africa, Europe China, Canada, Singapore, India)</td>
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BACK-UP CANDIDATES
The Company has utilized its’ proprietary screening method to examine a library of compounds and has identified new structures, in addition to MLR-1023, that are lyn kinase activators. At least two of the structures (3, 4) while patently distinct from MLR-1023 show topological similarities to MLR-1023 suggesting broad opportunities for a medicinal chemistry program aimed at designing back-up compounds to MLR-1023. The list of these structurally distinct compounds is summarized in Table 3.

Table 3. Summary of Compound Activities. Lyn kinase activation curves were run at different enzyme concentrations. Shown here are results for lyn enzyme at 200 ng/ml.

<table>
<thead>
<tr>
<th>COMPOUND</th>
<th>MOL. WT</th>
<th>LYN ACTIVATION</th>
<th>In Vitro EC₅₀ (µM)</th>
<th>OGTT EFFICACY</th>
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<td>MLR-1023</td>
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<td>4</td>
<td>279</td>
<td>Yes</td>
<td>0.5</td>
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CONTACT INFORMATION
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