

**CORPORATE HIGHLIGHTS**

- Providing safe and effective medicine to pediatric patients, parents and the healthcare professionals that serve them
- Pediatric, clinical and development expertise and pipeline
- Commercialization expertise
- Scientific and business expert advisory board in place
- Changing regulatory landscape – growing pediatric opportunities

**KEY MILESTONES**

- Partnership with Camargo Pharmaceutical Services established
- Secured initial \$1.2 MM funding
- Key development programs selected
- Feasibility studies completed – statin & analgesic
- Statin formulation developed - Q4 2008
- Patent filed for statin
- Secure additional \$2.0 MM funding, Q1 2010 - \$6.5 MM, Q4 2010
- Statin IND – Q2 2010
- Statin bioequivalence study – Q3 2010
- Statin NDA submission – Q3 2011
- Statin launch – Q3 2012
- Analgesic formulation development – TBD
- Analgesic IND – TBD
- Analgesic clinical studies – TBD

**About Madeira Therapeutics**

Madeira Therapeutics, LLC, is a privately held, specialty pharmaceutical company focused on providing safe and effective medicine to pediatric patients, parents and the healthcare professionals that serve them.

The Madeira strategy focuses on reformulating adult drugs for better dosage control in children. Madeira utilizes the FDA's 505(b)(2) approval method, which relies in part on the regulatory agency's findings for a drug previously approved for adults, thereby shortcutting NDA approval by years and saving tens of millions of dollars in development costs.

**MARKET RATIONALE**

There is a profound need for children's products that have been tested and approved safe and effective for use by children. In the period 1973–1997, the percentage of approved drugs that contained no labeling information for children remained fairly stable at 71–81%. More importantly, two-thirds of the drugs that are prescribed for children have not been studied and labeled for pediatric use.

With so few medicines containing adequate labeling information to guide their use, off-label prescribing has become an accepted practice. Off-label prescribing includes the use of a drug in unapproved indications, for an unapproved age group or utilizing an unapproved dosage, frequency or route of administration.

During their growth, children's metabolisms change and the pharmacokinetics or pharmacodynamics may differ from adults. Additionally, many of the drugs frequently used in infants and young children are not available in suitable dosage forms because they are available only as tablets, capsules or solutions for injection and not as a liquid formulation that has been studied in a pediatric population where the dose can be easily adjusted to a patient's age, size, gender and metabolism.

**ABOUT 505(b)(2)**

The marketing approval pathway for Madeira's products is the 505(b)(2) regulatory process established by the Food and Drug Administration (FDA). This approval process provides new pharmaceutical applications for changes to drugs that are of proven clinical efficacy and known safety since they are already on the market. The 505(b)(2) process involves studies of bioequivalence and usually small patient efficacy trials. Because the drug is already known, the clinical testing process is typically shorter and less costly than for a new drug compound where more extensive testing is required. The clinical testing process Madeira will use can be completed in as little as three years after the pre-IND FDA meeting.

**THE OPPORTUNITY**

With recent changes in the regulatory landscape regarding pediatric pharmaceuticals, the company believes that the opportunities are many and growing, and it is well positioned to take full advantage of these opportunities with pediatrics now established as the fastest growing prescription segment.

MADEIRA: DEVELOPMENT PIPELINE						
PRODUCT	2008	2009	2010	2011	2012	Potential Ped Market (\$ Millions)
Liquid Statin	Formulation Q4 Pre-IND complete	Complete Funding Q4	PK Study Q3	NDA Filing Q2	Launch Q3	\$1,100
Liquid Analgesic			TBD			\$250
Liquid Diabetes Others			TBD			\$2,000

Note: development timelines contingent upon \$2.0 MM financing Q1 2010



## MANAGEMENT & ADVISORY TEAM

### PETER R. JOINER, MBA

President & CEO (Founder)

- 30 years sales & marketing
- 15 major pharmaceutical product launches
- Sanofi-aventis, Merrell Dow, Alliant Pharmaceuticals
- Strategic business planning
- Executive level sales force management
- University of Cincinnati – B.A., M.B.A.

### KENNETH V. PHELPS

Chief Scientific Officer (Co-Founder)

- President & CEO, Camargo Pharmaceutical Services, LLC
- World expert in 505(b)(2) filings
- Executive level QC, regulatory affairs, clinical and medical affairs
- Executive level sales/marketing
- Sanofi-aventis, Merrell Dow, Eppley Center for Research, Duramed
- University of Nebraska – B.S. Chemistry

### CRAIG L. CHANCE, CPA

CFO

- Partner at Purinton, Chance and Mills, LLC, past 12 years
- 21 years financial and accounting for small/medium size businesses
- Member American Institute of Certified Public Accountants (AICPA)
- University of Kansas – B.A.

### LYLE J. BOOTMAN, PHD, SCD

Director/Advisor

- Dean of University of Arizona College of Pharmacy
- American Pharmacists Association, American Association of Pharmaceutical Scientists and the American College of Apothecaries
- Founder and executive director of the University of Arizona Center for Health Outcomes and PharmacoEconomic (HOPE) Research
- Former president American Pharmacists Association, president emeritus of the Pharmacy

### GREGORY KEARNS, PHARM.D, PHD

Director/Advisor

- Chairman of the Department of Medical Research
- Director Pediatric Pharmacology Research Unit at Children's Mercy Hospitals and Clinics
- First recipient of the Marion Merrell Dow/Missouri Chair in Pediatric Pharmacology at the University of Missouri-Kansas City, where he holds professional appointments in pediatrics and pharmacology

## Key Products in Development

### MT001 – CHOLESTEROL-LOWERING STATIN

In children and adolescents, hyperlipidemia may be secondary to associated conditions such as obesity, but heterozygous familial hypercholesterolemia (HeFH) is one of the most common and clearly documented conditions to have severe cardiovascular consequences beginning in childhood. Therefore, the identification and management of HeFH in children is of great consequence.

Five statins have been approved by the FDA for the treatment of children with HeFH who are at a markedly elevated risk of premature coronary artery disease. Several recent randomized, controlled clinical trials established both efficacy and safety of statin therapy in children ages 8 to 18 years with HeFH.

On July 1, 2008, the American Academy of Pediatrics (AAP) released its new policy statement on cholesterol in childhood. The new policy has taken on new urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension and cardiovascular disease (CVD) in older children and adults. Based on new data and extensive review, it is increasingly clear that cholesterol concentrations can be elevated during childhood and adolescence and that increased concentrations in childhood are associated with increased risk of atherosclerosis and CVD in adulthood. *For a further discussion of the AAP guidelines, see separate attachment.*

Having a statin formulation in liquid form for oral dosing allows for the necessary ability to customize the dose and individualize therapy according to the child's specific recommended goal. There are no current liquid statin drugs for children. The development of MT001 will provide for a statin in a suitable stable liquid dosage form and will be occurring at a time when the need for an appropriate liquid formulation for young children is greater than ever.

### MT003 – ACUTE PAIN RELIEVER

Acute pain due to illness, injury or medical procedure is the most common form of pain experienced by children. An increase in the number of children undergoing day-case pediatric surgery (e.g., dental extractions, tonsillectomy, adenotonsillectomy), and a tendency towards earlier discharge has led to the need for a safe, efficacious and potent analgesic oral solution for pain relief.

Currently, few potent analgesic medications are labeled for pediatric use and many children are not receiving therapeutic doses of pain medication. A study evaluating whether pediatric patients received therapeutic doses of pain medication provides support that pain management of infants and children is inadequate. Of the administered pain medication doses, 32% were in the therapeutic range, while 68% were either below or above the therapeutic range.

The analgesics used to treat acute pain in children currently include acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. The analgesic efficacy of acetaminophen and NSAIDs is often inadequate to treat pediatric post-operative pain, while the use of opioid analgesics for post-operative analgesia in children has been shown to significantly increase the time to, and reduce the amount of, rescue analgesia.

Ideally, an analgesic for acute pain in children should be available in an oral formulation with high potency, not cause respiratory depression and have a favorable adverse event profile. MT003, an analgesic oral solution with a potency intermediate between that of NSAIDs and opioids, will provide an effective and well tolerated analgesic in a suitable dosage form for the treatment of acute pain in children.

## COMPANY CONTACT

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## July 1, 2008, AAP Guidelines Summary

On July 1, 2008, the American Academy of Pediatrics (AAP) released its new policy statement on cholesterol in childhood. The new policy has taken on urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension and cardiovascular disease (CVD) in older children and adults.

Based on new data and extensive review, it is increasingly clear that cholesterol concentrations can be elevated during childhood and adolescence, and that increased concentrations in childhood are associated with increased risk of atherosclerosis and CVD in adulthood.

The AAP has released its new guidelines relating to the concentrations of LDL at which pharmacologic intervention is recommended for children 8 years and older and adolescents. They also recommend that pharmacologic intervention in children younger than 8 years only be implemented if they have the dramatic elevation of LDL concentration (>500 mg/dL) as seen with the homozygous form of familial hypercholesterolemia. The following table summarizes the new guidelines:

PATIENT CHARACTERISTICS	RECOMMENDED TREATMENT POINTS
No other risk factors for CVD	LDL concentration is persistently >190 mg/dL despite diet therapy
Other risk factors present, including obesity, hypertension, or cigarette smoking or positive family history of premature CVD	LDL concentration is persistently >160 mg/dL despite diet therapy
Children with diabetes mellitus	Pharmacologic treatment should be considered when LDL concentration is $\geq$ 130 mg/dL

## The Need for a Pediatric Statin

### A WHITE PAPER

by J. Lyle Bootman, PhD, ScD

#### INTRODUCTION

There are no pediatric dosages available for most medications allowing for the prescription of the right medicine, for the right patient and in the correct amount. Only about a quarter of all the drugs available for prescription contain labeling information for children, and more than two-thirds of the drugs that are prescribed to children have not been studied and labeled for pediatric use. As a result, off-label prescribing has become an accepted practice among physicians, leading to the prescription of extemporaneous formulations with untested bioavailability and stability in children.

One area of clear and immediate need is in the development of a statin product which can help children with genetic risks of developing early-onset heart disease. About one in 500 children have heterozygous familial hypercholesterolemia (HeFH), a condition resulting in severely elevated levels of plasma low-density lipoprotein (LDL-C). Left untreated, this condition has been clearly linked to early atherosclerotic lesions (fibrous plaques) and premature atherosclerosis and cardiovascular disease (CVD).

Development of a safe and effective cholesterol-lowering statin drug formulated specifically for children will allow early intervention. According to the American Academy of Pediatrics, this may make it possible to regress lesions to a degree that is not possible in later adulthood, significantly mitigating the risk of atherosclerosis.

#### PEDIATRIC DRUG DEVELOPMENT BACKGROUND

In recognition of the need for pediatric labeling instructions, Congress included incentives for conducting needed pediatric studies in the Food and Drug Administration Modernization Act of 1997 (FDAMA). When this failed to have significant impact, Congress passed the Best Pharmaceuticals for Children Act in January 2002, which provided the innovator a six-month extension to exclusivity if prescribed studies were performed. Later, in 2003, Congress passed the Pediatric Research Equity Act

which provided FDA with the authority to use bridging data from adult studies for the approval of pediatric medicines. Although the three acts are designed to encourage the development of pediatric drugs, to date, relatively few drugs are labeled for children.

While it is clear that some drugs are not applicable to children, it is often the case that the adult dose is too high for children. Children have different metabolisms and the pharmacokinetics or pharmacodynamics may differ significantly from adults.

In addition, many of the drugs frequently used in infants and young children are not available in suitable dosage forms. Most of the medications are available either as tablets, capsules or solutions for injection; however, young children frequently have difficulty swallowing the usual solid dosage form and these solid dosage forms are not easily titratable to a customized dose appropriate for a child whose size and metabolism at varying ages can greatly affect the efficacy of any given dose. Of greatest value in pediatric prescription is a liquid formulation that has been studied in children and can be easily titrated to the appropriate dose.

#### ABOUT HYPERLIPIDEMIA IN CHILDREN

In children, hyperlipidemia may be secondarily associated to conditions such as obesity, but extreme LDL elevations are usually associated with genetic factors. Of these, heterozygous familial hypercholesterolemia (HeFH) is one of the most common and the most clearly documented to have important cardiovascular consequences beginning in childhood.

HeFH has a prevalence of about one in 500 in Caucasian children and is characterized by defective LDL-C receptors, leading to severely elevated levels of LDL-C in the blood. Children as young as 8 with HeFH typically have total cholesterol levels in the range of 270 to 500 mg/dL. In studying children with HeFH, researchers have documented functional and morphological changes of the heart vessel wall, indicating that the atherosclerotic process has already begun. Children with HeFH are characterized by impaired function of the endothelium, the thin layer of cells that line the interior surface of blood vessels and the heart, and the thickening of arterial walls.

On the basis of this knowledge, on July 1, 2008, the American Academy of Pediatrics (AAP) released its



new policy statement on cholesterol in childhood. The new policy has taken on urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type 2 diabetes mellitus, hypertension and cardiovascular disease in older children and adults.

Based on new data and extensive review, it is increasingly clear that cholesterol concentrations can be elevated during childhood and adolescence, and that increased concentrations in childhood are associated with increased risk of atherosclerosis and CVD in adulthood.

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## CURRENT DEVELOPMENT STATUS

When a decision is made to begin drug treatment, initial therapy with a statin is recommended because bileacid binding resins and cholesterol absorption inhibitors (not yet studied in children) are usually inadequate alone to achieve sufficient LDL reduction. Four statins have been approved by the FDA for the treatment of children with HeFH who are at risk of pre-mature coronary artery disease, all in solid dosage forms. Several recent clinical trials have established both efficacy and safety of statin therapy in children with HeFH, aged 8 to 18 years. Reductions of LDL-C in the studies were quite similar to that for adults and showed no adverse impact on sexual or physical maturation.

Although the benefits are evident and these drugs are approved by the FDA, no statin is currently available in a suitable liquid dosage form for children. The practice of pill splitting to “adjust” doses is a common practice in adults, but pediatric physicians are hesitant to use this practice due to inaccurate splits leading to inappropriate doses.

## CONCLUSION

Lifestyle modification is the cornerstone of cardiovascular prevention in childhood and should remain so, but with one-third of U.S. children overweight and about 17% obese, the risk of early-onset CVD is unacceptable. Additionally, genetic factors such as HeFH mean we should be testing all children for high cholesterol levels and treating them both aggressively and as early as possible.

A statin product specifically formulated for children will be a powerful tool in preventing heart attacks when these children have reached their 40s and 50s. We are confident pediatricians everywhere will be eager to use this more appropriate statin formulation.

## MADEIRA THERAPEUTICS – CHOLESTEROL-LOWERING STATIN

Madeira Therapeutics in Leawood, KS, has a pediatric statin formulation in liquid form under development. For children it is recommended that stepped titration up to the maximum recommended dose is performed until target LDL levels are achieved or there is evidence of toxicity. Having a statin in oral formulation provides flexibility to customize the dose and individualize therapy according to the child’s specific needs. Approval is anticipated in 2011.

## Frequently Asked Questions and Answers: Media

### **Q: How is Madeira Therapeutics different than other drug development companies?**

**A:** We are a drug development company specializing in real pediatric medicine by reformulating compounds currently approved for adults with substantial safety and efficacy, and determining an accurate pediatric dosage and a child-appropriate delivery formulation. Madeira Therapeutics is one of the few drug development companies with a dedicated focus on this niche market—formulations that are sized to fit.

### **Q: Why focus on pediatric medicines?**

**A:** It is a case of true need—developing drugs with the appropriate safety, efficacy, and approval for children, and providing the education to physicians, lay medical staff and parents. Madeira Therapeutics is addressing the need for the right medication, for the right patient and in the right dosage form. Children metabolize drugs more rapidly than adults; our goal is to eliminate the inaccurate and scientifically untested “dosing down” of adult drugs for children based on weight.

Currently, greater than 70% of the drugs prescribed for children are not approved by the FDA.

### **Q: What process do you go through to determine if a compound is suitable for children?**

**A:** Madeira Therapeutics has over twenty criteria that we use to screen products. We determine if the drug makes sense from a medical standpoint and look at existing drugs to see if we think we can make something as good or better. We also look to see if there is anything in the pipeline at other companies that could represent competition. We determine if the drug will be stable in a liquid environment — we want drugs that are not easily stabilized in a liquid form, such that they will not be easily copied and we may be able to create intellectual property protection around the formulation process. Finally, we analyze approval requirements because we want to pick drugs that are affordable to develop versus those that could cost significantly more to reach approval.

### **Q: What is the first product? Others?**

**A:** The first compound in the development pipeline is a statin. It focuses on a case of need in a population with an inherited cholesterol gene that often leads to early heart disease. The second product in our pipeline is for acute chronic pain management.



**Q: Why aren't other drug development or pharmaceutical companies doing this?**

**A:** The expertise required to reformulate or reposition an adult drug is not very different from that required to develop a new chemical entity, i.e., a new drug.

This type of expertise is typically found at large pharmaceutical companies. These companies are not interested in this market because the opportunities here are generally in the \$50M to \$200M range per drug. This is too small for large pharma — they have significantly larger scale requirements — and smaller drug companies and generic drug companies don't have the expertise necessary for a 505(b)(2) type of approval.

Madeira Therapeutics has the world's leading expert on 505(b)(2) approvals, Ken Phelps, as our chief scientific officer.

**Q: How is the 505(b)(2) process different? It seems there is normally a long development time before a saleable product is achieved.**

**A:** For a new chemical entity (NCE) there are years spent conducting numerous studies in the development of a drug. However, the time to market for the compounds targeted by Madeira Therapeutics is actually quite short. We are working with already approved, existing drugs and "repositioning" them to meet the pediatric needs. The 505(b)(2) process speeds the approval process along considerably and reduces risk.



***Madeira: Sized to Fit.***  
*Real Pediatric Medicine*

[www.madeiratherapeutics.com](http://www.madeiratherapeutics.com)

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