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AOD9604 Shows Positive Results in an Animal Model of Osteoarthritis

- **AOD9604 has a positive effect on the repair of cartilage and joint tissue in an Osteoarthritis animal model**
- **Intra-articular injection of AOD9604 proven safe**

Calzada Ltd's ('Calzada') wholly owned subsidiary, Metabolic Pharmaceuticals Pty Ltd ('Metabolic'), is pleased to announce that it has received positive results from *in-vivo* tests conducted on AOD9604 at the Daegu Catholic University Medical Center, Daegu, Korea under the direction of Dr Dong Rak Kwon MD, PhD. These studies were conducted in a rabbit model of collagenase-induced Osteoarthritis (OA). This study was designed to explore the *in-vivo* potential of AOD9604 to treat OA, following the positive *in-vitro* results released in March 2012.

Key Research Findings
The animal study results provide evidence that:

1. AOD9604 has a positive effect on the repair of cartilage and joint tissue following intra-articular injection of AOD9604 into collagenase-induced OA in a rabbit model;

2. Hyaluronic Acid (HA), a drug commonly used in the treatment of OA in humans and animals and AOD9604 had an additive positive effect on the repair of cartilage and joint tissue following intra-articular injection of a combination AOD9604 & HA; and

3. There was no evidence of any adverse reactions in the joints of any of the AOD9604-treated animals.

Background to the Study
In March 2012 (ASX:13 March 2012 "AOD9604 Shows Positive Results in Cartilage and Muscle Repair Models"), Metabolic released positive results from *in-vitro* studies conducted by Professors Marc Grynpas and Rita Kandel at Mt Sinai Hospital in Toronto, Canada. Those research results provided evidence that AOD9604:

1. Has a positive (anabolic) effect on cartilage cells. AOD9604 was found to enhance key elements required for cartilage tissue formation by increasing the proteoglycan (cellular matrix) and collagen content of cartilage;

2. Enhances the differentiation of muscle progenitor cells (cells that create muscle cells) into muscle cells.

Given that OA is a disease that features damage to joints, including the cartilage, muscle and bone tissues and based on the study results above as well as the limited treatment options and a very large

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market size, Metabolic began a search for a suitable animal model to further develop AOD9604 for the OA application.

In 2010 Dr Kwon and co-workers published a paper in the Journal of Korean Medical Science *(2010; 25: 776-780)* titled "Additive Effects of Intra-articular Injection of Growth Hormone and Hyaluronic Acid in Rabbit Model of Collagenase-induced Osteoarthritis". In that study the co-injection of intra-articular HA and human Growth Hormone (hGH) was more effective than HA alone in the osteoarthritis model in terms of duration and severity of lameness, lower macroscopic scores of cartilage damage and histopathological scores of cartilage damage. In that study HA alone proved to be more effective than control (saline) on the same measures.

In light of the data from Profs Grynpas and Kandel, Metabolic asked Dr Kwon to collaborate on a similarly designed study to evaluate the effect of AOD9604 in the University Medical Center's model.

What These Results Mean

Dr Kwon's results confirm that the *in-vitro* results obtained by Professors Grynpas and Kandel are relevant in an *in-vivo* model of OA. This evidence gives Metabolic increased confidence that AOD9604 can be further developed to become an effective treatment for OA in both humans and companion animals.

In commenting on his study findings Dr Kwon MD, PhD said *"These results are exciting because they provide early stage evidence in a rabbit model that AOD9604 may help to repair OA damaged tissue. AOD9604 appears to have retained the same beneficial effects as hGH in our rabbit model of collagenase-induced OA. We encourage Metabolic to further develop AOD9604 as a potential treatment for OA."*

Potential Utility of AOD9604 in Osteoarthritis

This encouraging *in-vivo* efficacy data when combined with the highly favourable safety profile of AOD9604, proven in formal pre-clinical toxicology studies and six human clinical trials, provides strong rationale for use of the peptide to treat OA.

AOD9604 could offer further advantages in that it can be dosed in multiple forms including oral, transdermal, injection and intra-articular.

Furthermore depending on dose and delivery mechanism, due to AOD9604's substantial clinical safety data package, it is possible that human clinical trials for OA could commence at the phase 2 stage saving the company or any partner substantial time and money in the further development of AOD9604 for this indication.

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Target Osteoarthritis Market

The potential uses outlined above target support in conditions, trauma and injuries with very large markets and where there are limited or no adequate treatment options. For instance in the case of Osteoarthritis, this is the most common joint disease with 12.1% of US adults showing symptoms in the knee and obesity being associated with a 3.5 fold prevalence of OA in US adults between 60-64 years of age. (Medtrack database).

The majority of treatments only address the pain associated with OA, a market worth $4.521B in 2011 and expected to grow at a Compound Annual Growth Rate of 3.7% over the next eight years to reach $6.061B by 2019. Individual Hyaluronic acid products such as Synvisc (reduces pain and lubricates the damaged joint) had sales of $461m in 2011 (Medtrack database).

Intellectual Property

In December 2011 Metabolic lodged patent applications covering both the new cartilage and muscle applications of AOD9604 addressing both human and veterinary uses. These patents were merged into an expanded PCT application which was lodged on 7 December 2012.

Strategy

Metabolic will now move to provide this new OA animal data to a range of potential veterinary and pharmaceutical partners.

The company is reviewing strategic options for maximizing shareholder value from all the new and existing data.

Calzada is committed to seeking cost-effective approaches to building further significant value in AOD9604 and extracting value for shareholders from the >$50 m invested to date in the development of this proven safe peptide.

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About Calzada Ltd

Calzada has 100% ownership of PolyNovo Biomaterials Pty Ltd and Metabolic Pharmaceuticals Pty Ltd. The Company is listed on the Australian Securities Exchange (ASX Code CZD).

About PolyNovo Biomaterials Pty Ltd

PolyNovo owns and develops a suite of state of the art biodegradeable polymers that have potential applications across numerous medical fields. PolyNovo has licence agreements and alliances with a number of the world's leading medical device companies and also has joint venture arrangements with local experts in the areas of skin repair.

About Metabolic Pharmaceuticals Pty Ltd

Metabolic's major asset is the AOD9604 peptide which has potential applications in the treatment of obesity, bone, cartilage and muscle diseases and repair. AOD9604 is a small 16 amino acid peptide modelled on one active segment of human growth hormone. It has proven excellent safety and tolerability in a total of six human clinical trials involving 925 humans. In June 2012 AOD9604 received a self-affirmed GRAS status, conditional only on publication of the peptide's existing safety data. AOD9604 is being sold in the market as one of the key components of Phosphagenics' cosmetic anti-cellulite cream called BodyShaper™. Metabolic receives royalties from Phosphagenics on worldwide sales of this product and a share of any sub-licensing revenue that may be received.