



metabolic

ASX Announcement

ASX code: MBP

## Metabolic's neuropathic pain drug ACV1 – additional preclinical studies reveal greater potential

- Latest oral version of *ACV1* works as well as the injected version in new animal studies
- Provides proof-of-concept for Metabolic's *Oral Peptide Delivery Platform*
- An Independent study provides new knowledge about how *ACV1* works and reveals the likely biochemical target for *ACV1*

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Melbourne, 23 November, 2006:

### Oral version of ACV1 makes progress

Metabolic announced today substantial progress made in the use of Metabolic's *Oral Peptide Delivery Platform* to convert its injectable drug for neuropathic pain, *ACV1*, into an oral drug so that it can be swallowed rather than injected.

Metabolic has engineered an oral version of *ACV1* which, in several animal tests, has had analgesic effects equal to those seen with the injected drug. The latest oral variant of *ACV1* tested in animals results from optimisation of an earlier version (announced in February 2006), which showed good oral activity but was slightly less active than the injected form. A large batch of this new, fully active, oral version of *ACV1* is now being manufactured for further animal testing, and new patent applications are being filed. The Company hopes to progress this oral version of *ACV1* or a similar variant into a formal development programme in 2007.

Additionally, the creation of a fully functional oral version of *ACV1* provides proof-of-concept for the *Oral Peptide Delivery Platform* and further demonstrates Metabolic's extensive peptide engineering expertise. The knowledge gained from converting *ACV1* from an injected drug into an oral drug will assist Metabolic in testing its *Oral Peptide Delivery Platform* for application to other injected peptide drugs, such as insulin or parathyroid hormone. If the *Oral Peptide Delivery Platform* does prove to be applicable to other peptide drugs it could be a significant value driver for Metabolic. The result announced here for *ACV1* is a major step in that direction.

The development programme for an oral version of *ACV1* will run alongside the current Phase 2A clinical programme for the injected version of *ACV1*.

### Results from an independent study on ACV1 published in prestigious international journal

A key element in the clinical development and commercialisation of a drug with a novel mode of action is to understand how the drug works in the body (the mechanism of action) including in particular, which biochemical target in the body the drug acts upon. *ACV1* most likely acts by binding to and potentially blocking one of the hundred or more subtypes of a class of molecules in the body called nicotinic acetylcholine receptors (nAChR), but until now the particular subtype had not been identified.

A group of leading academic researchers working independently in the US recently identified the particular molecule in the body that *ACV1* potentially blocks, as well as significant additional information about how it may work to relieve pain and apparently repair damaged nerves. The results of this study have now been published and a paper will be printed in the prestigious journal, *Proceedings of the National Academy of Sciences of the United States of America* (PNAS). An advanced copy can be found at [www.pnas.org/cgi/reprint/0608715103](http://www.pnas.org/cgi/reprint/0608715103). These results, from an independent laboratory, add significantly to Metabolic's understanding of *ACV1* and therefore to its potential value.

The abovementioned paper explains that *ACV1* has potent blocking activity on the alpha9alpha10 subtype nicotinic acetylcholine receptor (nAChR), and that the alpha9alpha10 blockade may be responsible for the majority of *ACV1*'s alleviation of nerve hypersensitivity in animals. The researchers identified a substantial reduction in the accumulation of immune cells around the injured nerve, which may contribute to the protective and restorative properties of *ACV1*.

Metabolic's Chief Scientific Officer, Dr Chris Belyea, commented "the publication of this paper is exciting for us in many respects - it was independently conducted by scientists of the highest calibre, confirms the beneficial effects of *ACV1*, and reveals the likely biochemical target. Together with our progress in making an oral version of *ACV1*, this should substantially increase pharmaceutical industry interest in Metabolic's pioneering *ACV1* program and in our *Oral Peptide Delivery Platform*".

#### **Background to *ACV1* and neuropathic pain**

- *ACV1* was safe and well tolerated at all administered doses in the first human study (Phase 1 trial) for the drug, announced in November 2005.
- *ACV1* has been tested in several well-established animal pain models and shows efficacy in relieving the characteristic pain symptoms of neuropathy, allodynia and hyperalgesia.
- *ACV1* is a 16 amino acid peptide conotoxin derived from an Australian cone snail. The drug works by blocking a subtype of a class of receptors in the peripheral nervous system call neuronal nicotinic acetylcholine receptors (nAChR).
- Neuropathic pain is the most debilitating form of chronic pain, generated from damaged nerves and serving no beneficial function for the affected individual. Besides diabetes, the common causes of neuropathy are viral infection (e.g. shingles), trauma, sciatica, chemotherapy and various other conditions.
- Neuropathic pain affects 10 million people in the US alone. The current market for neuropathic pain drugs is valued at approximately US\$2.5 billion a year and is expected to double in five years.

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## About Metabolic

Metabolic Pharmaceuticals Limited (ASX: MBP, NASDAQ OTC: MBLPY) is a Melbourne based, ASX listed biotechnology company with 285 million shares on issue. The Company employs 24 staff and is led by an experienced and proven management team. Metabolic's main focus is to take innovative drugs, with large market potential, through formal preclinical and clinical development. Metabolic's expertise in drug development has resulted in two high value drugs in advanced human clinical development, namely:

- AOD9604 - an obesity drug currently in a Phase 2B trial with results expected in March 2007;
- AOD9604 - additional use in osteoporosis with a Phase 2 trial expected to commence in 2007; and
- ACV1 - a neuropathic pain drug currently in Phase 2A trials.

These drugs address multi-billion dollar markets which are poorly served by existing treatments. In addition to its lead drugs, Metabolic has an exciting research pipeline with drugs targeting type 2 diabetes (ADD) and nerve regeneration (NRPs). Metabolic is also developing a platform to enable oral delivery of existing injected peptide drugs, a technology which has already shown proof-of-concept. This has high potential for use by other companies developing peptide drugs and could foster multiple out-licensing deals.

Metabolic may license its lead drugs to a global partner following Phase 2 trials and will continue to utilise its clinical development expertise to drive future company growth and profits

For more information, please visit the company's website at [www.metabolic.com.au](http://www.metabolic.com.au).

## Background information on the drug development process

The steps required before a drug candidate is commercialised include:

1. Discovery or invention, then filing a patent application in Australia and worldwide;
2. Pre-clinical testing, laboratory and chemical process development and formulation studies;
3. Controlled human clinical trials to establish the safety and efficacy of the drug for its intended use;
4. Regulatory approval from the Therapeutic Goods Association (TGA) in Australia, the FDA in the USA and other agencies throughout the world; and
5. Marketing and sales.

The testing and approval process requires substantial time, effort, and financial resources and we cannot be certain that any approvals for any of our products will be granted on a timely basis, if at all.

Human clinical trials are typically conducted in three sequential phases which may overlap:

### Phase 1

Initial safety study in healthy human subjects or patients.

Phase 1 trials usually run for a short duration.

### Phase 2

Studies in a limited patient population designed to:

- identify possible adverse effects and safety risks in the patient population (2A);
- determine the efficacy of the product for specific targeted diseases (2B); and
- determine tolerance and optimal dosage (2B).

### Phase 3

Trials undertaken to further evaluate dosage and clinical efficacy and to further test for safety in an expanded patient population in clinical study sites throughout major target markets (e.g. USA, Europe and Australia).

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