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Partnering Prospects on AOD9604

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Correction of Australian Market Comments

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On 13 December, 2004 Metabolic Pharmaceuticals Limited (Metabolic) released the detailed results of its Phase 2b clinical trial on obesity drug AOD9604. There have been some comments which now need our response.

Prospects for partnering with major pharmaceutical companies

Metabolic's intention, armed with these Phase 2b proof-of-concept results, is to secure a partnership with a major pharmaceutical company to help fund further development and provide ultimate marketing and distribution of AOD9604.

Metabolic is very confident that the data will be of substantial interest to such companies due to the following key findings of the trial –

- Weight loss in line with competing products.
- Excellent tolerability without evidence of the major side effects of existing drugs
- Indications of accompanying health benefits
- Unique mode of action of AOD9604 which stimulates metabolism of body fat, compared with existing obesity drugs which artificially reduce appetite or food absorption.

We would not normally comment on the progress of early discussions. However in this circumstance we must advise that, within 24 hours of the announcement to the market, Metabolic received unsolicited requests for meetings and further data from several major international pharmaceutical companies with whom Metabolic has been discussing this project for over 1 year.

We expect to advance those discussions over the coming months.

Correction of Australian Market Comments

One analyst has made some errors of fact and interpretation and these have been relayed to others who have relied on them including the financial press. There have also been a few questions raised by others which warrant further comment. This has generated market uncertainty. Our comments, further to our very detailed announcement of the results, are provided below.

Weight Loss and statistical significance

Metabolic reported the key results provided by an independent statistician of both of the two statistical analyses of weight loss as prescribed in a Statistical Analysis Plan devised and finalised 6 months ago.

One analysis is called "primary" in the plan and another is "secondary". The primary analysis is used to design the required size and duration of the trial and the secondary analysis is exploratory. However both analyses are valid ways to assess weight loss.

On the results of the primary analysis, there is a 90% chance that the 1mg dose of AOD9604 induces weight loss. On the secondary analysis, there is greater than a 99% chance that the 1mg dose of AOD9604 induces weight loss. If the chance is greater than an industry standard of 95% the result is considered to be "statistically significant".

The primary method looks simply and directly at the difference between the week 12 and week 0 measurements. The secondary method of analysis is more sensitive because it assesses weight loss by using all the weight measurements made once every two weeks over the treatment period for each patient (including even for those patients who did not stay for the full 12 weeks) to essentially calculate an average "line of best fit" through the data points rather than relying only on the beginning and end.

In a Phase 3 trial, the last and definitive stage of clinical development, statistical significance on the primary analysis is typically required to gain marketing approval. However the trial Metabolic has just completed was not a Phase 3 trial. This was a Phase 2 trial designed to explore for an effective dose and provide the evidence sufficient to justify further development. This objective was achieved.

The analyst report and some newspaper reports stemming from it mention only the primary analysis and fail to mention the fact that, while the primary analysis method is slightly less than the industry standard of 95% confidence, the secondary analysis easily meets it.

Placebo weight loss

The same analyst writes that "*We are unclear of how significant a weight loss this actually represents because the spread of weight lost by those subjects on the placebo treatment is quite wide*". This is false. The spread of subjects in the placebo group and the number of patient who lost 4kg or more is normal and in line with the spread shown in

many other similar published studies on different drugs. Some people will always manage to lose weight by their own efforts.

In fact, the number of patients who lost 4kg or more on the 1mg AOS9604 dose was more than triple the number of patients who lost 4kg or more on the placebo dose.

This becomes more notable when considering people who lost even more weight. There were several people in all AOD9604 treated groups who lost large amounts of weight (8 kg or more and up to 21 kgs) compared to none in placebo.

Regulatory path

As stated in the announcement, Metabolic is planning to enter into Phase 3 in the second half of 2005, but with a lead-in period prior to the commencement of the Phase 3 to test doses of 1mg and lower. This is intended to confirm and identify the optimum dose. Once identified, dosing on the main study would commence at the best dose.

This lead-in period will add no more than a few months to the development path.

Metabolic is confident and our FDA consultant has confirmed that the results already in hand have sufficient efficacy data to satisfy the requirements of the FDA to undertake the Phase 3, preceded by the "lead-in" dose confirmation period.

Dose Response

Clinical trials very frequently produce surprises.

This is the first time in the world a drug with AOD9604's mechanism of action has been trialled, and to have some surprises when exploring a new mechanism is not unusual.

In this trial, one surprise was that the effective dose was the lowest dose tried, 1 mg. While it was a surprise, it was one of the possibilities entertained on biological grounds when we designed the trial. AOD9604 has been designed from the much larger human growth hormone molecule, and it is known that dosing with the equivalent number of molecules of human growth hormone would actually be a very high dose for that hormone. The result at 1mg AOD9604 suggests that AOD9604 operates very efficiently in humans, somewhat more efficiently than expected.

That the optimal result occurred with a low dose has very positive implications for cost of goods and ease of supplying a large market.

The 1mg dose showed average weight loss compared to placebo for both men and women, and in both obese and morbidly obese subgroups.

The weight loss effect did not rise with increasing dose. This was not a surprise, as all of Metabolic's previous animal and in vitro data indicated that doses above the optimum one would be less effective. Hormone mechanisms such as AOD9604 sometimes have these characteristics.

For men only, there was also a suggestion of a useful effect at higher doses. However the 1mg region is the most consistent and most promising.

This trial successfully identifies doses around 1mg or lower as being the best dose trialled. At this dose, the weight loss is competitive with existing drugs. It may well be that a dose lower than 1mg will work better. This will be determined in the planned further development.

About Metabolic

Metabolic Pharmaceuticals Limited is a biotechnology company based in Melbourne, Australia, and listed on the Australian Stock Exchange (ASX: MBP). The Company's mission is to develop a pipeline of new pharmaceuticals for world markets, and currently has active programs aimed at treating obesity (AOD9604 in development), pain (ACV1 in development) and type 2 diabetes.

Background to AOD9604

AOD9604 is a small orally active peptide modelled on one part of the human growth hormone molecule. Growth hormone naturally occurs in the body and has profound stimulatory effects on fat metabolism, with levels of the hormone typically becoming suppressed in the obese state. Replacement by daily dosing with AOD9604 is believed to reverse the suppressed fat metabolism.

Background to ACV1

ACV1 for neuropathic pain is the first in a potential new class of drugs to specifically treat neuropathic (nerve) pain. Current therapies rely largely on the 'off-label' use of anticonvulsants, antidepressants and local anaesthetics, which have unimpressive efficacy and dose-limiting side-effects. The potential range of indications for ACV1 extend to neuropathic pain in diabetics, post-herpetic neuralgia ("shingles"), sciatica and many other neuropathic pain conditions currently underserved by pharmaceutical treatment

ACV1 specifically blocks a subtype of a class of receptors in the peripheral nervous system called neuronal nicotinic acetylcholine receptors (nAChR). ACV1 can be administered by once daily subcutaneous injections providing substantial relief in several animal models of neuropathic pain without apparent adverse effect. Phase 1 clinical trials are planned for early 2005.

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