company announcement

Thursday 19 May 2005

# *Final report on MELANOTAN™ sustained release trial confirms excellent results*

Melbourne, Australia

EpiTan Limited (ASX: EPT, ADR: EPTNY, XETRA: UR9) today announced the release of final results of its Phase I/II dose escalation study (EP004), which began in November 2003 at Brisbane's Q-Pharm facilities. The trial was completed in January 2005. These final results confirm the interim results released on 15 December 2004.

The planned length of the trial was extended as a consequence of unexpected efficacy experienced in the first two cohorts when given MELANOTAN™ in sustained release implants. The trial was suspended for five months pending the receipt of new smaller implants containing a lower dose of the drug.

The trial involved 30 subjects in six cohorts. The first two cohorts (six people) received the original larger sustained release implants and four cohorts (24 people) received the new smaller implants.

The study compared blood levels, safety and efficacy of different levels of MELANOTAN™ administered subcutaneously (under the skin). The results of this study have also been used to predict and design the final commercial implant for testing in Phase III.

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## Summary of the results of EP004 trial

- MELANOTAN™ produced a statistically significant increase in melanin density in all doses used
- The minimum dose which achieved a maximum efficacy level was found
- Visible skin darkening (i.e. tanning) correlated with this dose
- Implant doses demonstrated enhanced safety, in both incidence and severity of adverse events, compared with EpiTan's two previous trials using daily liquid injections
- Melanin density levels were approximately double that observed in EpiTan's previous clinical trial (EP002) completed late in 2003, in which MELANOTAN™ was delivered via daily liquid injections

## Commentary

In the earlier EP002 trial it was shown that the melanin density increase produced by MELANOTAN™ contributed to a 50% reduction in UV-induced skin damage in fair skinned volunteers. The maximum increase in melanin density level achieved in this EP004 trial was approximately double that observed in EP002.

A significant improvement in overall safety and tolerability was demonstrated compared with results of previous studies involving daily injections (EP001 and EP002). There was a reduction in both the incidence and severity of adverse side effects in EP004 (see Appendix 1 for further details).

EpiTan discovered that when MELANOTAN™ is administered in a sustained release formulation a significant improvement in efficacy is achieved. As a result of this discovery, on 14 February 2005, EpiTan announced that it had filed a full international patent application covering these discoveries. The patent was filed to protect the use of MELANOTAN™ in all anticipated sustained release delivery formulations, including implant, topically, orally or other. EpiTan's intellectual property counsel confirmed that if this patent application is granted, EpiTan is likely to have 20 years of commercial exclusivity for MELANOTAN™, in sustained release delivery methods.

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Commenting on the final results, EpiTan's Managing Director, Iain Kirkwood said: "These results using a sustained release formulation delivered by a single injection are clearly excellent. Not only have we achieved a major improvement in efficacy, we have done so with a significantly improved safety and tolerability profile compared with earlier trials." He added: "We are naturally very pleased with the discovery which has lead to a full international patent application. We are looking forward to using these new implants in our next trials as the greater increase in melanin density may be able to show an even further reduction in UV-induced skin damage."

**Development of a final commercial implant**

Data collected in this trial has contributed to a predictive model developed by Professor Allan Evans and colleagues at the University of South Australia's Centre for Pharmaceutical Research. This model has assisted in the development of a clinically effective formulation of MELANOTAN™. EpiTan has commenced development of a final implant to be used in Phase III trials which are expected to commence in 2006.

**Photographic Records**

As part of the trial protocol, "before and after" photographs were taken. Following legal advice, for reasons of privacy and to ensure faithful colour reproduction (given the subject matter of the photographs), EpiTan is unable to include these photographs in this report, post them to its website nor widely distribute them.
These photos may be made available to be viewed on request and by personal appointment (contact investorrelations@epitan.com.au)

**Appendix 1: Detailed Results of EP004**

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| **Name of trial:** | Phase I/II dose escalation study of a single depot injection of MELANOTAN™ |
| **Location:** | Q-Pharm, Clive Berghofer Cancer Research Centre, Queensland |

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| **Blinding status:** | N/A (Open Study) |
| **Treatment method, route, frequency, dose levels:** | Implant injected subcutaneously in the upper arm. Doses ranged from 5mg to 40mg MELANOTAN™. Subjects were given only a single injection at the start of the trial. |
| **Number of trial subjects:** | 30 |
| **Dropout rate:** | 4 subjects requested the removal of implants in the first stage of the trial (larger implants) due to unexpected rapidity of onset and magnitude of skin tanning. These subjects were not removed from study because analysis of blood levels showed that MELANOTAN™ was fully delivered by this time. One subject failed to complete follow-up visits for analysis of pigmentation so was excluded from the efficacy analysis. |
| **Subject selection criteria:** | Healthy Caucasian adults aged between 18 and 70 |
| **Primary endpoint results:** | The primary objective was to determine the pharmacokinetics and tolerance of a slow-release formulation of MELANOTAN™. Pharmacokinetic analysis showed that the lowest dose delivered was below measurable quantitation levels of MELANOTAN™ in the blood and the increasing doses gave proportionately greater blood levels. *Exact pharmacokinetic and pharmacodynamic parameters are not given as they are commercial in confidence and the subject of EpiTan's international patent application.* Tolerance of the implant is given in the safety and tolerability section. |
| **Safety and tolerability:** | In general the implant was well tolerated. However four out of the six subjects from cohorts 1 and 2, who received the initial larger implant, requested removal of the implants as a result of a rapid and unexpected increase in skin pigmentation. Treatment emergent adverse events (>10%) for all subjects |

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| | included: (NOTE: No subjects received a placebo implant)<br>• 53% increased number of and darkening of freckles<br>• 47% mild headaches<br>• 20% mild nausea<br>• 17% mild fatigue<br>• 14% facial flushing<br><br>**Summary of safety and tolerability:**<br>Overall safety was greatly enhanced compared with earlier trials using daily injections (EP001 and EP002). Not only the incidence but also the severity of adverse events was reduced.<br>In EP004, 20% reported mild nausea and 14% facial flushing. All but one subject reported both nausea and facial flushing only on the day of receiving the implant. By comparison, in EP001 and EP002 81% subjects reported nausea (half of these were mild and half were moderate in severity) and 74% facial flushing. These events were in the main reported following daily injection of the drug.<br><br>In EP004 47% of subjects reported mild headaches. It should be noted however that in EP001 and EP002, 50% of the placebo (no MELANOTAN™) group also reported headaches.<br><br>In EP004, 53% of subjects reported increases in the number of and darkening of freckles which is related to the pigmentary action of the drug. Anecdotally, a number of the subjects reported that the freckles returned to pre-trial levels after the end of the study (4 months after they received the drug). |
| **Secondary endpoint(s) results:** | The secondary objective was to quantify serial changes in skin melanin density levels by reflectance spectrophotometry.<br><br>MELANOTAN™ produced a statistically significant increase in baseline corrected melanin density at the end of the study |

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| | with all doses used ($p<0.001$). The average maximum measured increase in melanin density was approximately double that in the previous clinical trial (EP002), in which MELANTON™ was administered by a regime of daily liquid injections.<br><br>Skin pigmentation was visibly apparent in the most efficacious doses. |

**About EpiTan**

EpiTan Limited is a Melbourne-based specialty pharmaceutical company with a strategy focused on growing a business centred on dermatology products.

The company's leading drug candidate, for which EpiTan holds exclusive worldwide rights, is MELANOTAN™ which is in clinical development. MELANOTAN™ is EpiTan's brand name for [Nle$^4$,D-Phe$^7$]-alpha-MSH, a synthetic analogue of the naturally occurring hormone alpha-MSH, which stimulates eumelanin production. EpiTan holds the rights to four other products for Australia and New Zealand; Linotar®, Exorex®, Zindaclin® and OraDisc™ A. Linotar and Exorex are in market. Zindaclin and OraDisc A are scheduled to be launched in late 2005 and 2006 respectively.

EpiTan is currently evaluating the in-licensing of other dermatology products to add to its portfolio.

**About MELANOTAN™**

MELANOTAN™ stimulates the body to make eumelanin, the dark pigment in the skin ("a tan") which is known to protect the body from skin damage as a result of exposure to ultraviolet (UV) radiation. UV radiation damage can cause sunburn and sunburn injury is widely recognised as a precursor to skin cancer. MELANOTAN™ stimulates eumelanin production without the need to expose the skin to UV radiation.

MELANOTAN™ has completed a Phase II clinical trial (daily liquid injections) in Australia which demonstrated that the drug reduced sunburn injury by up to 50% in fair-skinned volunteers. This represents a significant breakthrough for people most at risk of sunburn injury and skin cancer. EpiTan has expanded its clinical studies of MELANOTAN™ into Europe. These trials have two aims: to assess MELANOTAN™'s potential both as a preventative to reduce the effects of UV damage to skin and as a therapy for UV-associated skin disorders such as polymorphous light eruption (PMLE).

MELANOTAN™ has a number of delivery formulations in development. The most advanced is a sustained release injectable implant which is being used in current clinical trial programs.

An independent report commissioned by the company identified that there are two potentially lucrative markets for MELANOTAN™. Firstly, the prophylactic market which includes those fair-skinned populations that seek additional protection from UV damage because their levels of eumelanin do not normally increase when they are exposed to UV radiation. This may also include use by people who visit tanning salons. Secondly, the therapeutic market consisting of patients with UV-associated skin diseases or disorders for which MELANOTAN™ may provide a therapeutic benefit.

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