

## Clinical Appendix

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**The following additional information is provided in accordance with the Code of Best Practice for ASX Reporting by Life Science Companies.**

**Trial Title:** Randomised, multi-centre, efficacy evaluation of PI-88 in patients with hepatocellular carcinoma after hepatectomy – A Phase 2 Study

### **The Goal of the Trial:**

The trial was designed to explore the appropriate dosage and possible efficacy of PI-88 in reducing early tumour recurrence in patients who have had primary liver cancer tumours removed by surgery (curative hepatocellular carcinoma resection). The aim of these assessments was to collate enough information to make a decision to move to Phase 3 clinical development.

### **About the Phase 2 Trial:**

Randomised, multi-centre Simon-2-stage study design<sup>1</sup> with two treatment arms (two dose levels of PI-88), and an untreated control arm. Eligible patients who fulfilled the inclusion/exclusion criteria were randomised into three groups (A, B and C). Group A patients received standard of care but did not receive any treatment with PI-88, Group B patients received 160 mg of PI-88 and Group C patients 250 mg of PI-88, both via subcutaneous injection. The ratios of patient numbers in groups A:B:C was 1:1:1. Patients in the treated group received PI-88 for 9 treatment cycles (36 weeks) with a follow-up period of 12 weeks. Each 4-week treatment cycle comprised four consecutive daily doses of PI-88 per week for three weeks, followed by a one-week observation period (for a total of 12 injections per 28-day cycle). Patients in the untreated group entered the follow-up period automatically and returned to clinic every 6 weeks for 48 weeks, including the follow-up period.

The trial began in July 2005 and was conducted across six hospital sites in Taiwan.

The preliminary data analysis was conducted on all evaluable patients (168) at week 30. The stage 1 preliminary data were analyzed and publicly released in December 2006. The final data for stage 1 of the Phase 2 trial (at 48 weeks – comprising 36 weeks of treatment and a 12-week follow-up period) is the content of this data analysis. These final data are from the final cleaned and verified database.

### **Investigators:**

#### ***Principle Investigator:***

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#### ***Co-ordinating Investigators:***

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<sup>1</sup> Two-stage selection and testing design for comparative Clinical trials', Thall, PF, Simon, R and Ellenberg, SS. Biometrika(1988), 75, (2), 303-310

## Trial Endpoints:

**Primary Objective:** To explore the appropriate dosage and possible efficacy of PI-88 in patients with hepatocellular carcinoma following curative surgery.

**Secondary Objective:** To evaluate the safety and tolerability of PI-88 in patients with hepatocellular carcinoma following hepatectomy.

**Stage 1 Objective:** The purpose of the Stage 1 component of the 2-stage design was to select the dose for the second stage of the trial and the statistical analysis plan was defined to assess the appropriate dose based on a relative improvement in disease-free rate at 48 weeks.

## Methods:

Following curative hepatocellular carcinoma resection, 172 patients were randomised 1:1:1 to an untreated control arm, or to one of two PI-88 treatment groups to self-administer subcutaneously 160 or 250 mg/day for 4 days per week for 3 weeks in each 4-week cycle over 36 weeks. At the completion of treatment, patients were followed up over 12 weeks to assess disease-free rate and time to first recurrence (disease-free survival).

## Results:

**Primary Objective of stage 1:** The primary objective of stage 1 was the disease-free rate at 48 weeks with the statistical aim of selecting the dose for the stage 2 part of the design using the Simon two-stage design<sup>2</sup>.

$$T_1 = \frac{1}{\sqrt{2}} \max_{1 \leq j \leq 2} (Z_{j1} - Z_{01}) > y_1$$

Where  $y_1 = 0.500$  for selection of dose  $T_1 > 0.5$ .

In this study  $T_1$  for 160mg = 1.190. The  $T_1$  for Group B (160mg) is greater than the  $y_1$  value of 0.500, satisfying the end point of Stage 1.

### Implications of meeting the primary objective:

Based on meeting the primary objective, Stage 2 could commence according to the original protocol. However, due to the  $T_1$  value exceeding  $y_1$  by a factor of more than twofold, discontinuing Stage 2 of the original Phase 2 study and moving into Phase 3 study are warranted. Furthermore, previous discussions with the FDA support proceeding directly to Phase 3 rather than commencing the second stage of this Phase 2 trial. Stage 1 of this Phase 2 trial has identified 160 mg as an appropriate dose for further Phase 3 development of the product.

### Patient outcomes at 48 weeks:

Patient description at 48 weeks	Treatment arm: n (%)		
	Control	160 mg PI-88	250 mg PI-88
Evaluable patients	58	56	54
Experienced recurrence of disease	26 (45%)	16 (29%)	19 (35%)
Completed study disease free	29 (50%)	35 (63%)	22 (41%)
Dropped out of the protocol	3 (5%)	5 (9%)	13 (24%)

Analysis of the final 48-week data showed 160 mg of PI-88 to be safe and tolerable and showed that treated patients had an increase in the chance of remaining disease free.

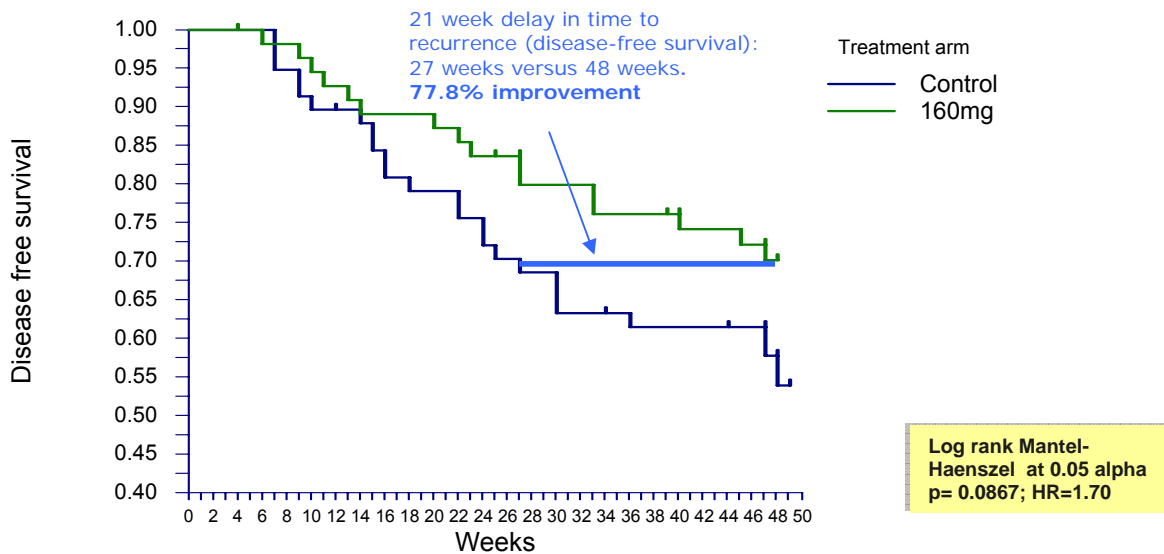
<sup>2</sup> Two-stage selection and testing design for comparative Clinical trials', Thall, PF, Simon, R and Ellenberg, SS. Biometrika(1988), 75, (2), 303-310

If untreated, patients had a 50 percent chance of remaining disease free by the end of the 48-week period

- ▶ The chance of remaining disease free is increased to 63 percent if patients were administered 160 mg of PI-88
- ▶ Treatment with the 250 mg dose resulted in thirteen patients terminating treatment early. This impacted the results seen from this treatment arm. The 250 mg dose of PI-88 reduced the disease-free rate by approximately 19 percent as compared to the control group, from 50 percent to 41 percent at 48 weeks

**Disease-Free Survival Efficacy Evaluation:**

A secondary endpoint of the trial was disease-free survival (ie the time a patient remains alive and free of disease). This endpoint removes drop-outs from the analysis. Disease-free survival is an important endpoint in itself but also because it will be used as a key design feature of the Phase 3 trial.



**Figure 1.** Disease-free survival comparing group treated with 160 mg of PI-88 to the untreated control group

- ▶ The time to tumour recurrence improved by 78 percent in patients receiving 160 mg of PI-88 compared to untreated patients (to 48 weeks from 27 weeks)
- ▶ Patients treated with the 250 mg dose of PI-88 were inseparable from the control

**Serious Adverse Event (SAE) Analysis:**

- 4 SAEs were reported as possibly related to treatment: Gum bleeding, HCC recurrence with tumour rupture, Intracerebral haemorrhage, Extra-hepatic recurrence and tumour rupture with internal bleeding;
- 4 SAEs reported as unlikely related to treatment: Carbuncle over right middle back, Hyperkalaemia, Hemorrhoid, and Hepatic Encephalopathy with Upper GI Bleeding; and
- 13 SAEs were reported as unrelated to treatment: Gastrointestinal Bleeding, Right Pelvic Bone Fracture, Severe Vomiting & Dizziness, Myocardial Infarction, Pneumonia with Respiratory Failure, Lower Leg Oedema, Adhesion Ileus, Hypoglycaemia, Colles fracture and calcaneus fracture, MCA Infarction, Acute pancreatitis & adhesion ileus, Gastric Ulcer with Bleeding and Severe Ascites

**Discontinued patient analysis and implications:**

Tolerability is an important measure in clinical trials and, in this Phase 2 clinical trial, we have established that the dose of 160 mg given in the prescribed schedule is safer and more effective than the 250 mg dose.

**Analysis of drop-outs (21 of a total of 172 patients):**

Treatment group (number of drop-outs)	Reason for dropping out
Control (3)	<ul style="list-style-type: none"> <li>▪ Intercurrent illness - SAE Right pelvic fracture with upper GI bleeding</li> <li>▪ Intercurrent illness - Nasopharyngeal carcinoma</li> <li>▪ Withdrawal of consent</li> </ul>
160 mg (5)	<ul style="list-style-type: none"> <li>▪ 2 - withdrawal of consent</li> <li>▪ SAE - Myocardial Infarction</li> <li>▪ CTC toxicity - SAE Hepatic encephalopathy with upper GI bleeding</li> <li>▪ CTC toxicity - Grade 3 to 4 ALT</li> </ul>
250 mg (13)	<ul style="list-style-type: none"> <li>▪ 1 - Upper gastro-intestinal bleeding</li> <li>▪ 3 - severe adverse events (possibly related) – Grade 3 neutropenia, gum bleeding, Intracerebral haemorrhage</li> <li>▪ 2 - thrombocytopenia** (1 Grade 2 and 1 Grade 3)</li> <li>▪ 6 - Grade 3 ALT. Early termination due to cessation of PI-88 treatment for more than 3 weeks (2 considered unrelated)</li> <li>▪ 1 - unrelated acute pancreatitis &amp; adhesion ileus</li> </ul>

\*ALT is an enzyme that is normally found in the liver and in the blood. ALT activity in blood is used to screen for liver damage. Grade 3 is considered a severe and undesirable adverse event

\*\*Low levels of platelets, specialised blood cells involved in clotting

**Implications of the Results:**

These results demonstrate that a dose of 160 mg of PI-88 has a good safety profile. The encouraging trend identified in the disease-free survival analysis (see Figure 1) is important because these data will be used as a critical design feature of the Phase 3 trial for registration. At 48 weeks, approximately 50 percent of the patients in the untreated control arm were disease free, as compared to 63 percent of patients treated with PI-88 at a dose of 160mg. The delay in time to recurrence (disease-free survival) was extended by 78 percent (27 weeks to 48 weeks) for the patients treated with 160 mg of PI-88.

The 250mg dose of PI-88 reduced the disease-free rate as compared to the control group, was inseparable from the control group as to disease-free survival, and was associated with an appreciably greater drop-out rate, partly attributable to tolerability factors. As a result, the company has elected to move only the 160mg dose into Phase 3 further clinical development at this stage.