

## **Appendix – Detailed Clinical Trial Information**

**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 Phase 2 Liver Cancer Trial:**

The trial was designed to assess the efficacy and safety of PI-88 given at two different doses to patients who have had primary liver cancer tumours removed by surgery (curative hepatocellular carcinoma resection).

### **About the Phase 2 trial:**

Randomised, multi-centre study 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 did not receive any treatment, Group B patients received 160 mg/day of PI-88 and Group C patients 250 mg/day of PI-88. 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 28-day treatment cycle contained three 1-week consecutive treatment periods followed by a 1-week observation period. Patients in the untreated groups will enter the follow-up period automatically and return to clinic every 6 weeks for 48 weeks.

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

The preliminary data analysis was conducted on all evaluable patients (168) at week 30. The final data for the Phase 2 trial (at 48 weeks – comprising 36 weeks of treatment and a 12-week follow-up period) are expected to be available by the second quarter of 2007, once the final data from all trial sites have been verified, analysed and the study report is written and filed with regulatory agencies in the USA and Taiwan. The final data will add to and build on the 30-week results described in this document.

### **Investigators:**

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

Dr. Pei-Jer Chen, Internal Medicine, National Taiwan University Hospital

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

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### **Trial endpoints:**

#### ***Primary Objective:***

To evaluate the efficacy of PI-88 in patients with hepatocellular carcinoma following hepatectomy.

#### ***Secondary Objective:***

To evaluate the safety of PI-88 in patients with hepatocellular carcinoma following hepatectomy.

**Methods:**

Following curative hepatocellular carcinoma resection, 172 eligible patients were randomised 1:1:1 to an untreated control arm, or to 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 are to be followed up over 12 weeks to assess recurrence rate and time to first recurrence (disease-free survival).

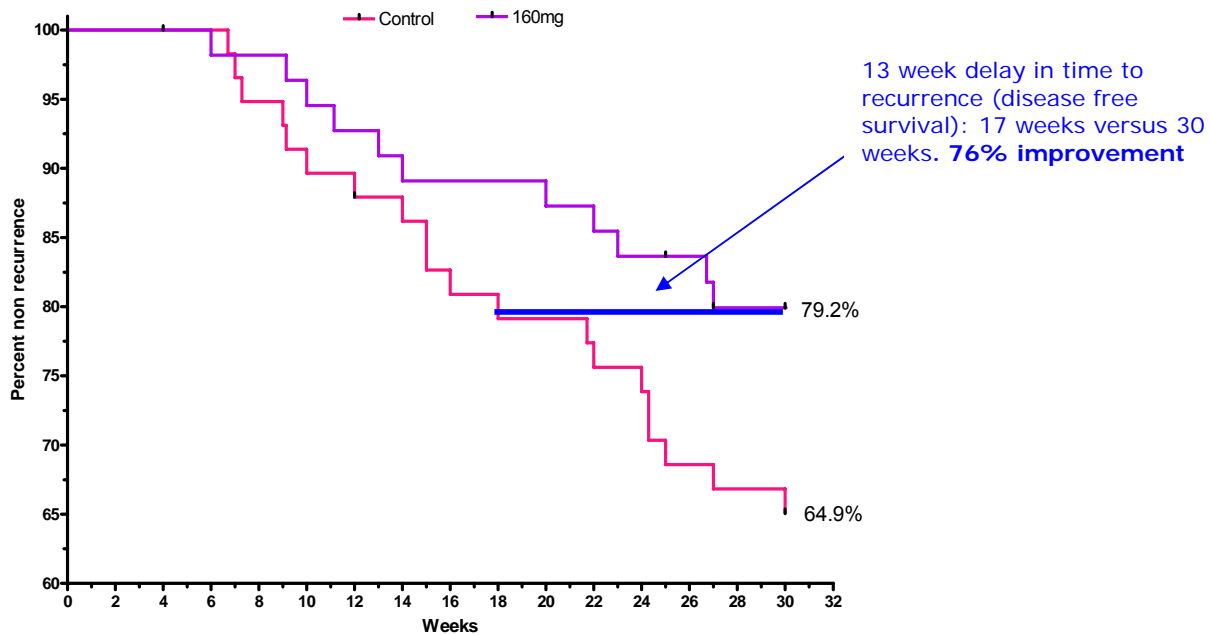
**Patient outcomes at 30 weeks**

Patient description at 30 weeks	Treatment arm		
	Control	160 mg PI-88	250 mg PI-88
Evaluable patients	58	56	54
Experienced recurrence of disease	20	11	12
Completed study disease free	37	42	30
Dropped out of the protocol	1	3	12

**The preliminary results:**

Analysis of the 30-week data showed that patients within the control and 160 mg arms demonstrate a similar safety and tolerability profile, but treated patients showed (1) an increase in the chance of remaining disease free and (2) a prolongation of time to first tumour recurrence.

- ▶ If untreated, patients had a 65% chance of remaining disease-free by the end of the 30-week period
- ▶ The chance of remaining disease free is increased to 79% if patients are administer 160 mg of PI-88
- ▶ The time to tumour recurrence improved by 76% in patients receiving 160 mg of PI-88 compared to untreated untreated patients (to 30 weeks from 17 weeks)



**Figure 1. Time to recurrence comparing group treated with 160 mg of PI-88 to the untreated control group**

**Implications of trial data:**

These results demonstrate that a dose of 160 mg of PI-88 has a good safety profile. The encouraging trend identified in the time to recurrence analysis (see Figure 1) is important because these data will be used to design the statistically powered Phase 3 trial for registration. At 17 weeks, approximately 80 percent of the patients in the untreated control arm were disease free. This time was extended by 76% (17 weeks to 30 weeks) for the patients treated with 160 mg of PI-88.

**Implications of drop-out analysis:**

Difficulty with tolerability is a normal feature of clinical trials and in this Phase 2 clinical trial, we have now 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 (16 of a total of 172 patients)***

Treatment group (number of drop-outs)	Reason for dropping out
Control (1)	<ul style="list-style-type: none"> <li>▪ Withdrawal of consent</li> </ul>
160 mg (3)	<ul style="list-style-type: none"> <li>▪ 2 - withdrawal of consent</li> <li>▪ 1 - Grade 3 ALT*. Early termination due to cessation of PI-88 treatment for more than 3 weeks</li> </ul>
250 mg (12)	<ul style="list-style-type: none"> <li>▪ 1 - early termination due to concomitant drug - Aspirin for cerebral infarction</li> <li>▪ 2 - severe adverse events (possibly related) – Grade 3 neutropenia, gum bleeding</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