



## **ASX Announcement**

### **Dia-B announces results of Phase I human trial for type 2 diabetes drug ISF402, and progress toward Phase II trials**

**6 December 2007:** Diabetes development company Dia-B Tech Limited (ASX:DIA) today announced that based on very encouraging completed Phase I clinical results of its novel drug ISF402, for the treatment of type 2 diabetes, it will commence planning for the Phase II stage of clinical development.

Dia-B has previously announced:

- an excellent tolerability profile for ISF402 in humans with no adverse clinical effects
- that ISF402 has proven oral availability, which contrasts with most peptides that are broken down and destroyed in the stomach
- an assay for the detection of ISF402 in human plasma

Dia-B has now received an interim report analysing the pharmacodynamics and pharmacokinetics of ISF402 in healthy volunteers and patients with type 2 diabetes, which confirms encouraging dose response trends in the key metabolic parameters, plasma insulin and C-peptide (an indicator of insulin release).

Dia-B Chairman, Dr Michael Wooldridge said, "These results in humans are consistent with the extensive work we performed in pre-clinical animal trials. The report shows very encouraging trends to support the continued development of this drug. We are in the process of designing a product development plan to meet the requirements of opening an Investigational New Drug (IND) application with the US FDA to fully comply with the FDA regulatory regime."

The Phase I study design was a single centre, double-blind, one-way pharmacokinetic study in 32 healthy male volunteers (stage A) and 11 subjects with type 2 diabetes (stage B).

In stage A, there were linear dose response trends in the key metabolic parameters, plasma insulin and C-peptide. In stage B, conducted in people with diabetes, there were trends towards lower blood glucose, lower basal C-peptide and higher increases in C-peptide after a standard meal, but these did not reach statistical significance. However, given the small sample size in this study, the absence of statistical significance was not unexpected.

Dr Wooldridge noted, "This will be a specific focus of a much larger Phase II trial. The trends in these key measurements are in the right direction and the Board finds them very encouraging."

Professor Paul Zimmet AO, a co-inventor of ISF402 and Chairman of the Scientific Advisory Board said “Phase I clinical trials are performed primarily to establish the safety and tolerability of a new drug and these objectives were achieved. It is encouraging to see positive trends in insulin and C-peptide and lower blood glucose after a standard meal in some of the patients with type 2 diabetes when given ISF402 compared to placebo. We now look forward to seeing Dia-B perform a larger study at a range of doses to confirm these effects.”

“Our earlier analysis of pharmacokinetic data showed rapid absorption of the drug. A large body of research suggests that poor control of post-meal blood sugars is a major risk factor for heart disease in people suffering from diabetes and so rapid absorption of the drug would be a very important benefit of ISF402 therapy,” said Professor Zimmet.

Professor Zimmet added, “There are a number of safety concerns with the currently available drugs for treating type 2 diabetes. We are hopeful that ISF402 may mean such concerns become a thing of the past.”

Dr Wooldridge said, “Dia-B will look to join a small and elite number of Australian companies that have drugs proceeding to Phase II human trials. We anticipate commencing dosing of patients in late 2008.”

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## **About Dia-B Tech:**

Dia-B is an Australian publicly listed biotechnology company (ASX:DIA) focused on the development of therapeutics for the treatment of type 2 diabetes and its associated complications. Type 2 diabetes is suffered by 90% of all people with diabetes and essentially occurs when insulin produced in the body does not fully work. Dia-B has three compounds in development:

- ISF402, an orally administered diabetes treatment just completed Phase 1 trials
- IM014 in preclinical development as an insulin sensitiser
- CDA1 in preclinical development for diabetic nephropathy and atherosclerosis

Diabetes is a major metabolic disease now regarded as reaching epidemic proportions in the developed world. In Australia there are real concerns about the likely social and economic burden and this has motivated federal, state and territory governments to agree on a \$200 million program to tackle the disease. In the USA more than 20 million people have diabetes representing 7% of the population.

## **Forward Looking Statements**

This press release contains forward-looking statements that reflect the Company's current expectations regarding future events. Forward-looking statements involve risks and uncertainties. Actual events could differ materially from those projected herein and depend on a number of factors including the success of the Company's research strategy, the applicability of the discoveries made therein, the successful and timely completion of clinical studies and the uncertainties related to the regulatory process.

## **Appendix: Analysis of Pharmacodynamic data from a Phase I trial of ISF402.**

**Clinical Trial Protocol Number: DIAB-ISF402-001**

### **Background on ISF402**

ISF402 is an analogue of an endogenous tetrapeptide. The proposed mechanism of action includes activation of the insulin signalling pathway directly as well as influencing the dispersal and/or clearance of injected insulin. ISF402 lowers blood glucose when injected alone and can stimulate the insulin signalling pathway in muscle cell-lines in the absence of insulin. Direct activation of insulin signalling differentiates the mechanism of insulin sensitisation by ISF402 from the thiazolidinedione class of insulin sensitisers, which enhance insulin-mediated activation of PI-3 kinase but do not activate PI-3 kinase independently. In the fasting state, these activities lead to a significant decrease in plasma C-peptide concentrations, which is indicative of reduced insulin secretion. Thus ISF402 has two activities that influence insulin action, insulin dispersal/clearance and activation of the insulin signalling pathway.

ISF402 is a 4 amino acid peptide with the amino acid sequence Val-His-Thr-Asp-amide (or VHTD-amide). It is metabolised to HTD-amide (abbreviated to HTD), which is the active molecule *in vivo*, so HTD is the molecule of interest for bio-analytical and pharmacokinetic analysis.

### **The objectives of the study:**

To determine the pharmacokinetics of ISF402 following a single oral dose in healthy volunteers and Type 2 diabetic patients.

To determine the pharmacodynamics of ISF402 when administered as a single dose in Type 2 diabetic patients one hour before receiving a standard calorie controlled meal.

### **Previous interim reports:**

Results for the primary objectives of safety, tolerability and pharmacokinetics have been reported previously. Briefly, ISF402 was well tolerated and there were no adverse events attributable to the drug. Absorption into the circulation after oral dosing with ISF402 was confirmed by measurement of the active metabolite HTD in plasma, which was detected in all subjects dosed at the highest dose level.

In this latest report a secondary outcome of pharmacodynamics using the markers, blood glucose, insulin and c-peptide (a marker of insulin secretion), was analysed. This was performed in an attempt to detect signs of biological activity of ISF402 in humans. Because the study was primarily designed to analyse safety, tolerability and pharmacokinetics, statistical significance in the pharmacodynamics are unlikely, but trends that will assist in the design of future studies may be detected.

## **Study Design:**

### Stage A

A single centre, double-blind, one-way pharmacokinetic study in 32 healthy male volunteers was undertaken. Four cohorts of 8 healthy volunteers (cohorts 1-5) were randomised to receive an initial starting dose of 100 mg ISF402 or placebo, with a dose escalation to 1600mg. The safety and tolerability of each cohort was reviewed prior to dose escalation to the next treatment. There was no intra-subject dose escalation. Blood and urine samples will be collected for the first 24 hours.

### Stage B

A single-centre, double-blind pharmacokinetic study in 16 exercise or diet controlled type 2 diabetic subjects. Two cohorts of 8 exercise or diet controlled Type 2 diabetic subjects were randomly assigned to receive either ISF402 or placebo in Period 1. They returned to the clinic 14 days later and received the opposite treatment in Period 2. One hour following ISF402 or placebo, volunteers were administered a standard calorie controlled meal.

*A protocol change resulted in 11 patients being enrolled in Stage B.*

The formulations tested were as follows:

Test formulation: ISF402 solution in water

Reference Product: Sodium bicarbonate in water

A 900 mg dose of ISF402 was selected for Stage B based on the safety and pharmacodynamic data from Stage A.

*This paper reports on the pharmacodynamics of ISF402 following oral administration of a single dose. Stages A and B will be analysed separately.*

## **Pharmacodynamic Analysis: Methods**

The pharmacodynamic results from Trial DIAB-ISF402-001 were processed according to standard non-compartmental analytical procedures. The software used was Microsoft Excel Professional Edition 2003 and WinNonlin v 5.2 (Pharsight Corporation USA). Plots were constructed in Microsoft Excel Professional Edition 2003.

The concentrations of glucose, insulin and c-peptide were measured in blood samples from all subjects. The pharmacodynamic analysis involved analysis of a concentration-time profile of blood glucose, insulin and c-peptide levels in volunteers following the dose of ISF402.

The quantitative comparison of the pharmacodynamics between parameter (glucose, insulin, c-peptide) and placebo involved:

### **Glucose: Stage A and Stage B**

- C<sub>max</sub> (maximum observed concentration)
- T<sub>max</sub> (time to reach maximum observed concentration, without interpolation)
- C<sub>baseline</sub> (fasting blood glucose level at pre-dose)
- C<sub>nadir</sub> (concentration at the maximum glycemic reaction observed during the dosing episode)
- T<sub>nadir</sub> (time to nadir)

To minimise the complicated inter-subject variation in basal glucose levels, normalisation of the pharmacodynamic parameters was undertaken. Hence the following parameters were tabulated for each subject at each dose level (Stage A) and at each period (Stage B).

- % Fall in glucose nadir at each dose level relative to baseline:  $(C_{\text{basal glucose}} - C_{\text{nadir glucose}} / C_{\text{basal glucose}}) \times 100$

- AUC (effect)glucose: subtract AUC glucose from AUC basal (where AUC glucose is calculated by the trapezoidal rule and AUCbasal is calculated by multiplication of C<sub>basal</sub> glucose and T<sub>last</sub>). This is also referred to as AUC<sub>net</sub>.

In addition, in Stage B, where blood glucose profiles were more complex due to the administration of a meal one hour post dose, and where it is known that the proposed mechanism of action results in a lowering of blood glucose, additional AUC effect data was gathered. This was to account for the glucose level falling below the baseline as well as quantifying that remaining above the baseline.

### **Insulin and C-peptide**

C baseline insulin (fasting insulin concentration at pre-dose)

C baseline C-peptide (fasting c-peptide concentration at pre-dose)

- C<sub>max</sub> (maximum observed concentration)
- T<sub>max</sub> (time to reach maximum observed concentration, without interpolation)
- AUC<sub>basal</sub>: (assumed to be constant for each subject and will be calculated by basal level x T<sub>last</sub>)
- AUC<sub>insulin</sub> (area under the concentration-time curve from time 0 to T<sub>last</sub>, where T<sub>last</sub> is the sampling time of the last measurable insulin concentration, calculated using the trapezoidal rule)
- AUC<sub>c-peptide</sub> (area under the concentration-time curve from time 0 to T<sub>last</sub>, where T<sub>last</sub> is the sampling time of the last measurable c-peptide concentration, calculated using the trapezoidal rule)
- AUC (effect) insulin and AUC(effect)c-peptide : (integrated area between plasma insulin or c-peptide concentration and the respective basal plasma levels)

e.g AUC (effect) insulin = AUC<sub>insulin</sub> –AUC basal

e.g. ΔAUC (effect) c-peptide = AUC c-peptide –AUC basal

## **Results Stage A: Dose escalation in healthy volunteers**

### **Glucose**

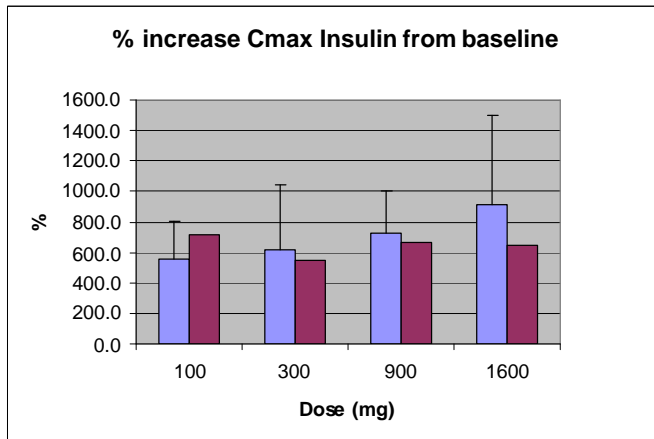
There was no pattern in terms of dose dependency for glucose pharmacodynamics. At all four dose levels, the glucose-time profiles were similar in shape. When inter-individual variability was taken into account, there was no statistically significant difference between profiles at any dose levels.

### **Plasma Insulin**

Insulin level versus time illustrated a similar profile for all dose levels (including placebo). Despite significant variability, a linear relationship ( $R^2 = 0.995$ ) existed between % increase in C<sub>max</sub> from baseline versus dose (Figure 1). This is in contrast to the insulin profile obtained following placebo administration where no clear pattern was evident. However, given the small sample size (n=6 at each dose level for ISF402 and n=2 for placebo) a larger study (more subjects) is required to confirm this relationship.

Nevertheless, an increase in ISF402 dose tends to increase the insulin levels at around 6 hours, which in this case was post meal. High variability for all other parameters preclude any similar relationships being drawn with dose.

Figure 1



### C-peptide

There does not appear to be a relationship between ISF402 dose and % fall in C<sub>adir</sub> or AUC effect. There is a tendency toward a dose-% increase C<sub>max</sub> above baseline (Figure 2). Notwithstanding the small sample sizes for each dose (n=6) and placebo (n=2) at each dose level, it is possible to discern an apparent linear relationship between dose and % increase C<sub>max</sub> above baseline which is not observable for placebo (Figure 2, Panel A). This results in an R<sup>2</sup> value of 0.6945 on regression of the mean values at each dose level (Figure 2, Panel B).

Figure 2A

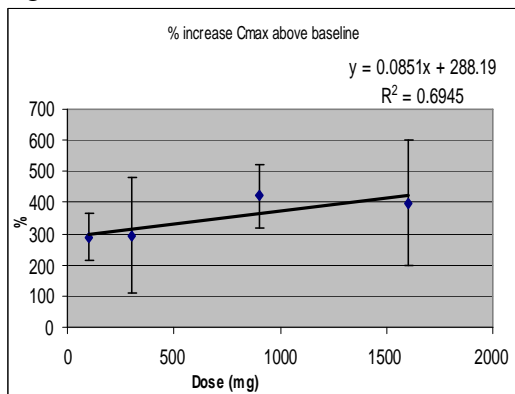
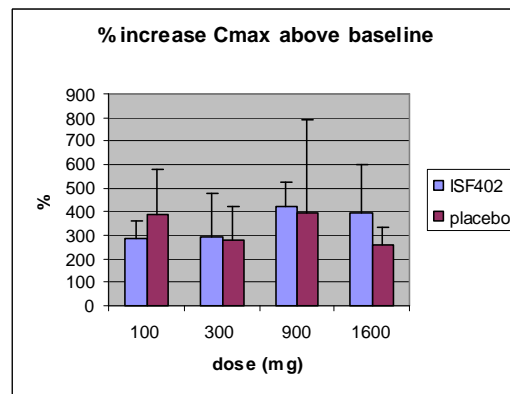


Figure 2B



### Discussion Stage A

The pharmacodynamic analysis undertaken in Stage A did not detect statistically significant differences in glucose, insulin and C-peptide due to the low number of subjects and high variability. Since the study was primarily designed to assess safety, identification of significant differences in these parameters was not expected.

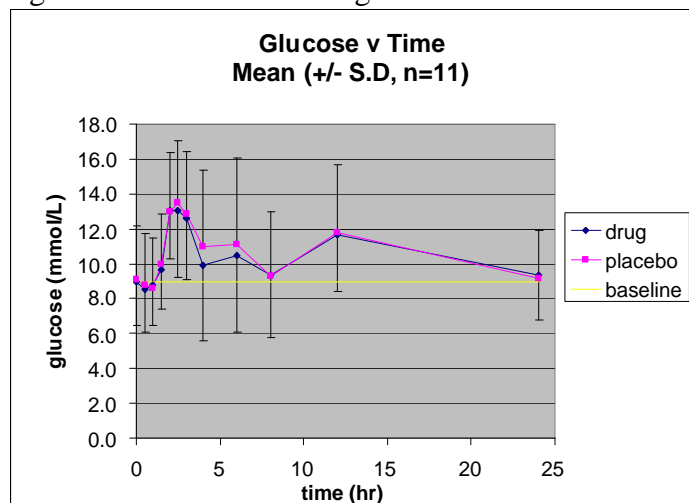
Analysis of insulin and C-peptide across the cohorts identified a linear relationship between % increase C<sub>max</sub> v dose level, where the highest dose tends to produce the greatest percentage increase in C<sub>max</sub> relative to baseline. A larger study (more subjects) is required to confirm this relationship.

## Results: Stage B Cross-over study in diabetic patients, n=11

### Glucose

The mean profile of glucose following drug (ISF402) and placebo administration is presented in Figure 3. There is considerable overlap between the profiles generated following administration of ISF402 and placebo, indicating a lack of significant difference between the two administrations. It is apparent that mean glucose levels for diabetic patients (Stage B) are higher than for healthy volunteers (Stage A).

Figure 3 Glucose levels Stage B



A number of patients showed a fall in glucose levels following administration of the drug or placebo relative to baseline. This differed from the less variable data obtained for 900 mg ISF402 given to healthy volunteers in Stage A. Hence it was necessary to conduct the pharmacodynamic analysis differently for these patients, to account for areas (AUC) both above and below the baseline and the time spent at these levels (Tables 1 and 2).

Overall the AUC above base line was lower and AUC below base line was higher for ISF402 compared to placebo, which would be expected for glucose lowering by the drug. However, these changes were not statistically significant, which was not expected given the small size of the group ( $p > 0.35$  for AUC above baseline, AUC below baseline, AUCnet (AUCbaseline-AUCcurve), time above B, time below B, % time below B).

Table 1: AUCeffect data: ISF402 Stage B

	baseline	AUC above B	AUC below B	AUC net	time above B	time below B	% time below B
<b>ISF402</b>							
Mean	9.0	36.3	3.3	33.1	17.1	5.0	22.7
S.D	2.5	25.0	5.3	28.4	6.5	4.8	21.1
<b>Placebo</b>							
Mean	9.1	39.4	2.4	37.0	19.9	4.1	17.1
S.D	3.1	18.9	4.7	22.2	5.8	5.8	24.0
P=	0.70	0.72	0.38	0.66	0.35	0.62	0.61

NOTE: P-values obtained by applying a two-sided paired t-test to results obtained in both tables 1 and 2.

### Insulin

No significant differences were noted between insulin pharmacodynamic parameters including AUC effect for ISF402 and placebo administrations.

### C-Peptide

No significant differences were noted between C-peptide pharmacodynamic parameters including AUC effect for ISF402 and placebo administrations. Notwithstanding the small sample sizes there was a tendency toward a % increase Cmax above baseline (p=0.16), which reflected both a lower baseline and higher Cmax for ISF402 compared to placebo (Table 2). A larger study (more subjects) is required to confirm this effect.

Table 2 C-peptide: Stage B

Parameter	ISF402 mean	SD	Placebo mean	SD	TTEST P value
Cmax	4003	770	3786	696	0.27
Tmax	5.6	1.4	5.7	1.3	0.84
Cnadir	1076	253	1126	329	0.29
Tnadir	3.0	7.0	3.0	7.0	0.99
Cbaseline	1094	315	1207	359	0.20
% fall Cnadir from baseline	-0.3	13.9	5.4	14.3	0.41
% increase Cmax	286.6	107.3	235.2	103.2	0.16

### Discussion Stage B

The pharmacodynamic analysis undertaken in Stage B did not detect statistically significant differences in glucose, insulin and C-peptide due to the low number of subjects and high variability. Since the study was primarily designed to assess safety, identification of significant differences in these parameters was not expected. There was a tendency toward a greater % increase Cmax above baseline for ISF402 compared to placebo (p=0.16), which reflected both a lower baseline and higher Cmax for ISF402. This is consistent with a trend towards increased Cmax above baseline for plasma c-peptide with increasing dose that was observed in stage A of the study. A larger study (more subjects) is required to confirm this effect.