13 December 2004

AOD9604 Phase 2b Clinical Trial Successful

- **Effectively induces weight loss.**
- **Excellent tolerability.**
- **Beneficial changes in lipids and glucose consistent with weight loss.**
- **Low effective dose beneficial for manufacturing capacity and cost of goods.**

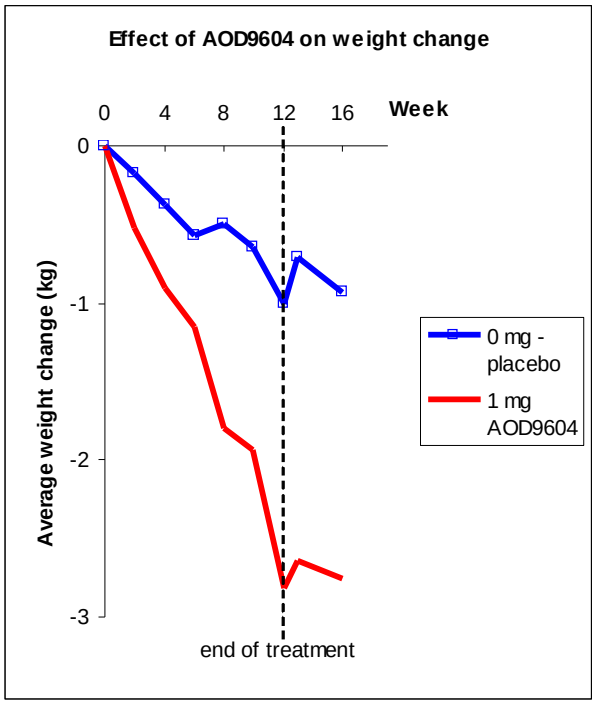
We are delighted to announce successful results from our Phase 2b clinical trial on obesity drug AOD9604. Over the 12 weeks of treatment AOD9604 induced weight loss and showed excellent tolerability.

About the study

Three hundred obese patients were enrolled in a double-blind randomised placebo-controlled trial. Each patient was given the same general diet and exercise advice. Six different dose levels of once daily oral dosing with AOD9604 were tested: 0 mg (placebo), 1 mg, 5 mg, 10 mg, 20 mg and 30 mg, over 12 weeks.

Key outcomes

The 1mg dose group was the most effective. In this dose group, the weight loss was similar to that achieved with currently available prescription drugs, with a superior tolerability profile. The average weight loss over the 12 weeks was more than triple placebo, 2.8 kg compared to 0.8 kg for placebo. The rate of weight loss with AOD9604 was statistically significantly compared to placebo.



The weight loss rate was maintained throughout the 12 week treatment period, an encouraging trend for expectations of longer term dosing.

AOD9604 showed excellent tolerability at all doses. Existing drugs have well documented side effects, limiting their popularity.

There were also indications of health benefits associated with the AOD9604-enhanced weight

loss. In the groups receiving AOD9604, there were beneficial trends on glucose tolerance and lipid profiles consistent with the magnitude of weight loss.

Commentary

Prof Gary Wittert, Principal Investigator on the study said: "The results from this clinical trial successfully demonstrate that once daily oral administration of AOD9604 induces weight loss. Over the duration of this study, the magnitude of the weight loss is roughly that which would be expected from currently available drugs. The drug was well tolerated, and there were metabolic benefits consistent with the weight loss".

"In this 12 week proof of concept study, weight was still being lost at an undiminished rate at the end of the treatment period, and the longer term pivotal studies will determine the maximum benefits that can be achieved. As the world's first drug with a metabolic mechanism of action, AOD9604 could occupy a unique position in the options available to doctors for the management of obesity."

"It is important to emphasise that, from the outset of the invention and its development from the laboratory bench, this has been an all Australian effort, and in the context of the clinical trial program and I am grateful to my co-investigators Profs Proietto, and Strauss in Melbourne, Prof Caterson in Sydney, and Prof Prins and Dr Stocks Brisbane, for their efforts."

Prof Louis J Aronne MD, President of the North American Association for the Study of Obesity and a member of Metabolic's US Clinical Advisory Panel, said "This is an exciting new approach to a problem which has defied easy solutions. We will need many different treatments if we are going to manage obesity successfully, in much the same way we have many treatments available for diabetes and hypertension. Unlike currently available treatments which rely on reducing calorie intake, this one appears to work primarily on metabolic pathways and merits further investigation".

Prof Michael Jensen MD is an expert on lipid metabolism, a past president of the North American Association for the Study of Obesity, and a member of Metabolic's US Clinical Advisory Panel. He said "The scientific idea behind AOD9604 is an elegant one and completely different from the existing approaches to obesity. The interesting trial results reported here by Metabolic clearly justify further development and I look forward to seeing the future outcome."

Dr Frank Ng of Monash University, the inventor, said "I am delighted to see my scientific research confirmed in humans and being applied to this enormous public health problem. I congratulate Metabolic's professional and committed development team for their fruitful efforts."

Chris Belyea, CEO of Metabolic, said "These results prove that our commitment to developing this unique drug was justified. AOD9604 works. In this trial it delivered competitive weight loss with better tolerability, along with positive health benefits and encouraging indications for longer term dosing. As the first in its class, AOD9604 is well positioned to provide a clear competitive advantage in the large and growing obesity medication market."

Further development plans

With successful demonstration of proof of concept, Metabolic's focus now advances to two key activities:

- planning for commencement of worldwide pivotal Phase 3 trials in the second half of 2005; and

- securing a partnership with a major pharmaceutical company for the Phase 3 development and marketing.

The low effective dose has enormous positive benefits for the cost of manufactured goods and the ease of supplying a large market. Doses lower than 1 mg need to be explored to find the optimum dose, and this can be done as a lead-in component to the Phase 3 clinical study. We will be discussing the design with the US and European regulatory authorities.

Acknowledgements

Metabolic's first thanks go to the 300 patients who participated. Metabolic would also like to thank the investigators and staff at the five clinical trial sites throughout Australia for their interest, advice and exceptional commitment in undertaking this study.

This trial was supported by a START grant of A$2.1 million from AusIndustry.

Further Details

The appendix to this announcement provides technical details of the trial and its results, intended for the specialist technical audience.

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.

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APPENDIX AOD9604 PHASE 2B Clinical Trial Results

In accordance with the ASX Draft Code of Best Practice on reporting for Biotech companies, this section contains detailed preliminary analysis of the results of the trial, intended for the biotechnology and medical professional audience.

General

Trial Description A Phase 2b clinical trial to assess efficacy and tolerability of daily oral dosing of AOD9604 over 12 weeks

Study Conduct The study was conducted at 5 clinical trial sites in Australia according to the principles of Good Clinical Practice (ICH GCP). The principal investigator was Prof Gary Wittert of the University of Adelaide, and the conduct of the trial including data collection and analysis was coordinated by Kendle Australia Pty Ltd.

Study Design The trial was randomised, double-blind and placebo-controlled. Three hundred obese males and females were enrolled in the trial and provided with general diet and exercise advice. The patients were randomly assigned to one of six dose groups – each group receiving capsules containing either 0, 1, 5, 10, 20 or 30 mg AOD9604 for once daily dosing over 12 weeks. The patients visited the clinic every two weeks for monitoring. There were follow-up visits at one week, 4 weeks and 12 weeks after dosing finished. The blind was broken after completion of the 4 week follow-up. This analysis reports the data up to that point.

Primary Endpoints The primary endpoints (aims) of the trial were to assess safety and tolerability and whether AOD9604 causes weight and/or fat loss.

Patient Selection criteria Obese males or females of non-child bearing potential with a Body Mass Index of 35 or more, aged 30 to 65 and otherwise healthy.

Demographics of Trial Participants Starting Active Treatment

Average Age	44 years
Gender	129 Females, 154 Males
Average BMI*	42 kg/m^2
Average Weight	122 kg

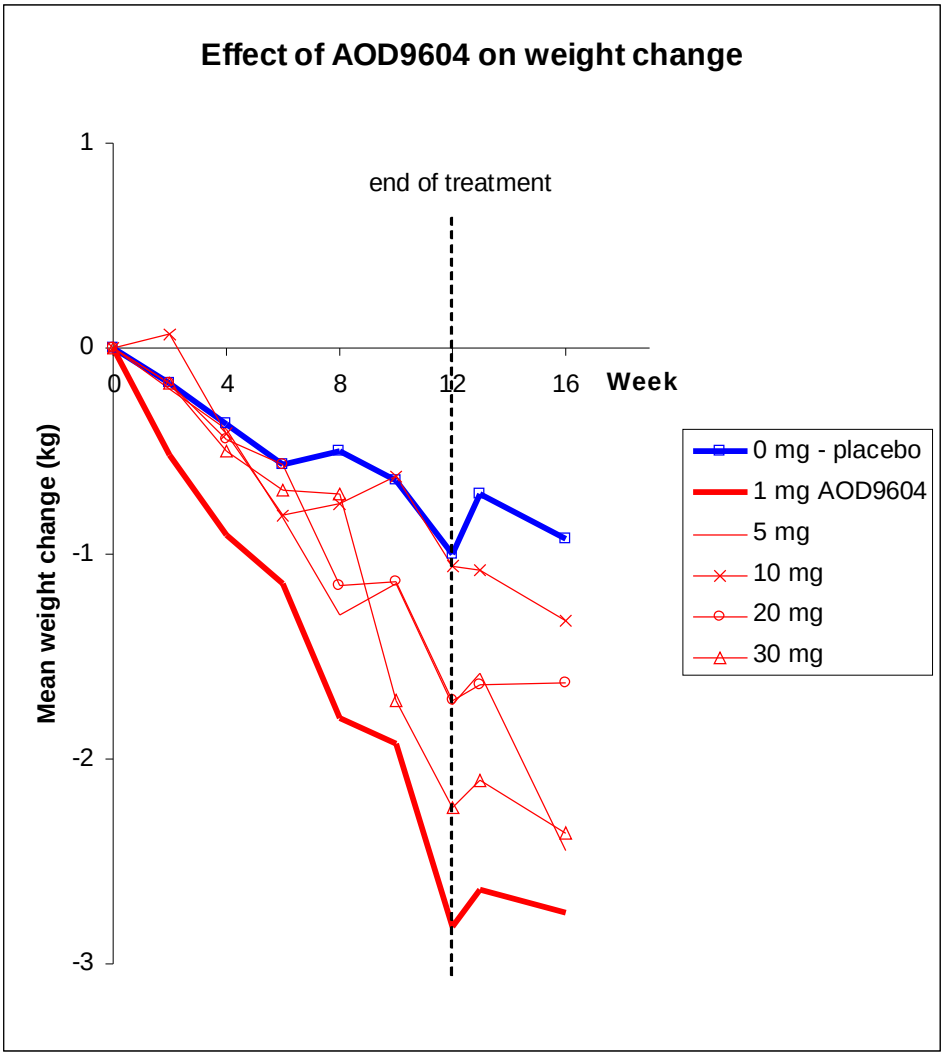
* Body Mass Index = weight in kg divided by the square of height in metres

Dropout Rate There was no significant difference in the dropout rate between groups.

	AOD9604 Dose group					
	0 mg (Placebo)	**1mg**	**5 mg**	**10 mg**	**20 mg**	**30 mg**
No. Started treatment	45	48	47	46	50	47
No. Completed Week 12	37	34	37	41	47	32

Weight loss

Summary The lowest dose group, 1mg, showed the best effect, 2.0 kg more than placebo. The rate of weight loss was sustained and there was no evidence of rebound weight gain after treatment compared to placebo.



Statistical analysis: There were two analyses of weight change in the predetermined plan to assess statistical significance. The primary analysis was based on the difference between weight at the start and at Week 12 for each dose group, compared to placebo. A secondary and confirmatory analysis was to use all the weight measurements taken every two weeks over the 12 weeks to calculate the slope of the line of best fit – i.e. the rate of weight change for each patient. The result of the primary analysis was near significance for the 1 mg dose group compared to placebo. The secondary analysis of rate of weight change gave high statistical significance for the 1mg dose group ($p<0.0001$), strongly supporting the effectiveness of this dose. The statistician has concluded that these data are consistent with 1mg being an active dose.

Weight change – primary analysis using Week 0 and Week 12 weight measurements	**AOD9604 Dose group**					
	0 mg (Placebo)	**1mg**	**5 mg**	**10 mg**	**20 mg**	**30 mg**
Week 12 weight minus Week 0 weight (kg) ± SEM*	**-0.8** ±0.6	**-2.8** ±0.7	**-1.6** ±0.6	**-1.0** ±0.6	**-1.7** ±0.6	**-2.2** ±0.7
P-value compared to placebo**	-	**0.10**	0.84	1.00	0.73	0.44

* Adjusted means and standard errors from the general linear model
**Dunnett's multiple comparisons procedure

Weight change – secondary analysis using all weight measurements	**AOD9604 Dose group**					
	0 mg (Placebo)	**1mg**	**5 mg**	**10 mg**	**20 mg**	**30 mg**
Rate of weight change relative to placebo (kg/day)	-	-0.0199	-0.0038	0.0013	-0.0085	-0.0105
P-value compared to placebo*	-	**<0.0001**	0.29	0.70	**0.015**	**0.005**

*A general linear model was fitted with weight as the dependent variable, time (days) as a covariate and treatment as a factor. The estimate of rate of weight loss was derived from the parameter for time*treatment. The correlation between the repeated measurements on the same individual were incorporated in the model.

Comparison with existing drugs – efficacy The overall weight loss over 12 weeks in excess of placebo (2.0 kg) was slightly more than published data for the market leader Xenical® (1.8 kg). The second placed drug, appetite suppressant Meridia®, records slightly more weight loss but is less popular due to its adverse effects on heart rate. In terms of longer term efficacy, a major limitation of all current obesity drugs so far tested is that their effect slows down over time, to the point that after about 7-8 months, there is no further weight loss, the excess over placebo typically maximising at 5 to 6 kgs. AOD9604 is the first drug to act on normalising fat metabolism rather than reducing dietary intake. Whether AOD9604's novel mechanism avoids the long term slow down will be revealed in the future longer term pivotal study.

Weight loss distribution The 1 mg dose group showed a consistently higher percentage of people losing weight, both for small or large amounts. The probability of losing 4kg or more was tripled. In the higher dose groups, the effect of the drug was still evident but was typically restricted to a few people, mainly men, who received substantial benefit.

		AOD9604 Dose group					
		0 mg (placebo)	**1 mg**	**5 mg**	**10 mg**	**20 mg**	**30 mg**
% of subjects losing more than a certain weight*	**Any weight**	**65%**	**82%**	**59%**	**66%**	**67%**	**72%**
	2 kg or more	**35%**	**50%**	**32%**	**24%**	**36%**	**44%**
	4 kg or more	**8%**	**26%**	**16%**	**7%**	**19%**	**28%**
	8 kg or more	**0%**	**9%**	**8%**	**5%**	**7%**	**9%**

* Intention to Treat - All data

Fat Loss

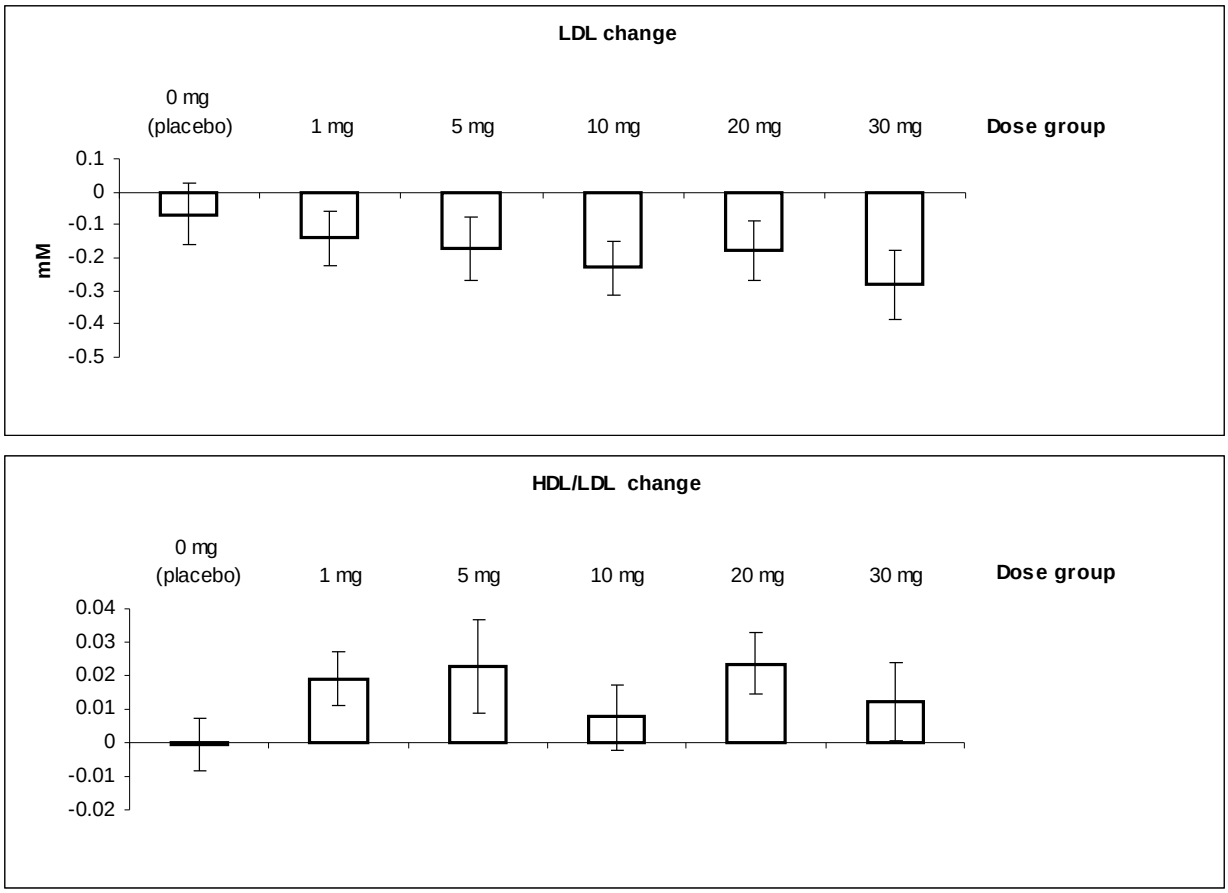
Computer tomography analysis of the abdomen was used to measure fat loss. These methods are inherently more variable than weight, but the trends are consistent with AOD9604 causing fat loss from the abdomen.

Week 12 minus week 0 ± SEM	AOD9604 Dose group					
	0 mg (Placebo)	**1mg**	**5 mg**	**10 mg**	**20 mg**	**30 mg**
Sagittal height* (cm) ±SEM	**-0.1** ± 0.3	**-0.7** ± 0.3	**-1.3** ± 0.3	**-0.4** ± 0.3	**-1.1** ± 0.3	**-0.4** ± 0.3
Abdominal circumference(cm)± SEM**	**+0.6** ± 0.8	**-1.3** ± 0.8	**-1.8** ± 0.8	**-1.3** ± 0.7	**-2.0** ± 0.8	**-1.1** ± 0.9
Abdominal fat area (cm^2) ± SEM	**-23** ± 15	**-35** ± 15	**-48** ± 14	**-41** ± 13	**-48** ± 14	**-40** ± 15

* cross-sectional distance from the back to the front of the waist.
** waistline

Lipids

Obesity is associated with unhealthy cholesterol profiles, a major risk factor in cardiovascular disease. There was a small but consistent trend to improvement in cholesterol profiles with AOD9604 compared to placebo – a beneficial reduction in LDL ("bad cholesterol") and a beneficial increase in the ratio of HDL ("good cholesterol") to LDL.



Week 12 minus week 0 ± SEM	AOD9604 Dose group					
	0 mg (Placebo)	1mg	5 mg	10 mg	20 mg	30 mg
Triglycerides (mM)	-0.25 ± 0.07	-0.14 ± 0.07	-0.12 ± 0.12	-0.10 ± 0.20	-0.15 ± 0.09	-0.30 ± 0.20
Total Cholesterol (mM)	0.01 ± 0.09	-0.02 ± 0.10	-0.07 ± 0.10	-0.17 ± 0.09	-0.18 ± 0.11	-0.28 ± 0.10
HDL Cholesterol (mM)	-0.01 ± 0.02	0.02 ± 0.02	0.01 ± 0.02	-0.04 ± 0.03	-0.02 ± 0.02	-0.05 ± 0.02
LDL Cholesterol (mM)	-0.07 ± 0.07	-0.14 ± 0.08	-0.13 ± 0.09	-0.25 ± 0.08	-0.21 ± 0.09	-0.28 ± 0.10
NEFA (mM)	0.01 ± 0.02	0.01 ± 0.02	-0.01 ± 0.03	-0.03 ± 0.03	-0.00 ± 0.02	-0.08 ± 0.04

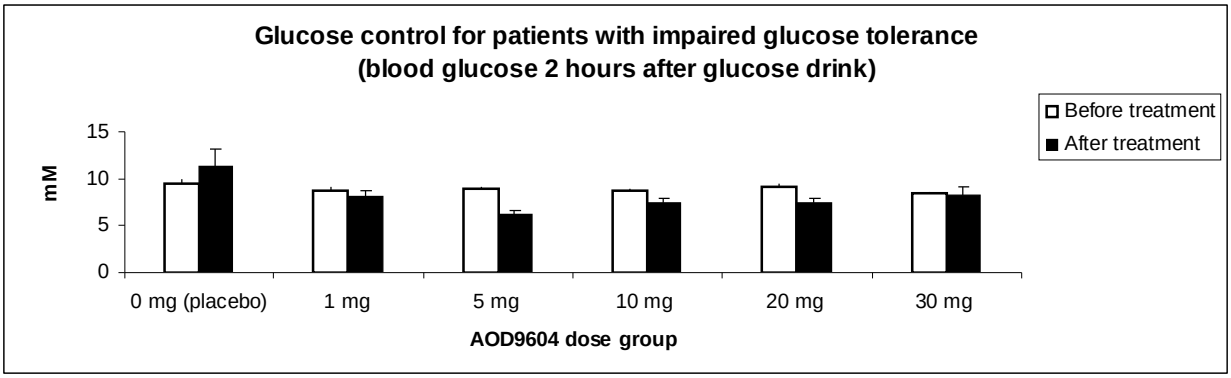
Glucose Control

The risk of impaired glucose tolerance ("IGT") and diabetes is greatly increased in obesity. In this study, people testing as having impaired glucose tolerance at the start were allowed to participate, but those testing as diabetic were not.

AOD9604 treated groups all had a reduced number of patients with IGT or diabetes at the end of the study compared to the start. This did not happen in the placebo group. In addition, most of the positive tests for diabetes at the end of the trial occurred in the placebo group.

Total number of patients testing with diabetes** or IGT*		
AOD9604 Dose Group	**Before treatment**	**After treatment**
0 mg (Placebo)	**7**	**7 (5 of these with diabetes)**
1mg	13	9 (1 of these with diabetes)
5mg	5	3 (1 of these with diabetes)
10mg	17	12 (none with diabetes)
20mg	13	7 (none with diabetes)
30mg	10	7 (2 of these with diabetes)

* IGT defined as blood glucose two hours after glucose drink between 7.9 and 11 mM
** Diabetes defined at fasting blood glucose of 7.0 mM or greater or blood glucose two hours after glucose drink greater than 11 mM

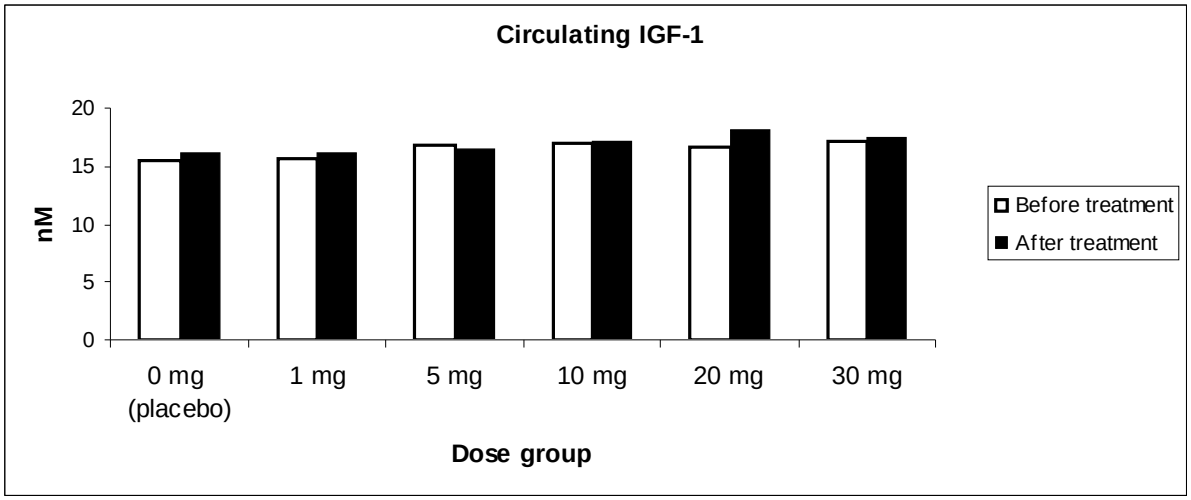


ECG and Vital Signs

All ECGs and vital signs, including heart rate, blood pressure, temperature, and respiration rate remained unchanged, with a trend to improvement in systolic blood pressure in the 1mg and 30mg AOD9604 groups, consistent with the weight loss.

IGF-1

Circulating levels of the hormone IGF-1 are elevated by the action of growth hormone. IGF-1 is the key mediator of the growth effects of growth hormone. The principle of action of AOD9604 is that it retains the fat metabolic benefits of growth hormone without the adverse growth and other effects associated with elevated levels of circulating IGF-1. This trial conclusively proves that AOD9604 does not elevate circulating IGF-1.



Quality of Life

The SF-36 questionnaire was used to assess the patients' perceived quality of life. There was no specific effect of AOD9604 on this measure - all dose groups including placebo generally showed a small trend to improvement in perceptions of both mental and physical quality of life.

Serious Adverse Events

There were no serious adverse events related to the drug.

Adverse Events

AOD9604 showed excellent tolerability. The incidence of adverse events was similar in all dose groups including placebo, and were of a character typically noted in placebo groups in clinical trials.

Antibodies

No antibodies to AOD9604 were detected in any patient.

END of APPENDIX