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An Open-Label Pilot Study to Assess the Safety and Potential of Oral Insulin to Reduce Liver Fat Content in Patients with Nonalcoholic Steatohepatitis (NASH)

ORA-D-N01
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Confidential

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are global public health issues closely associated with the worldwide epidemics of diabetes and obesity.[1-3] NAFLD encompasses the spectrum of liver disease in patients with no significant alcohol consumption ranging from fatty liver to steatohepatitis and cirrhosis.[1] Nonalcoholic fatty liver (NAFL) is characterized by the presence of liver infiltration of fat (hepatic steatosis) with no evidence of hepatocellular injury in the form of ballooning of hepatocytes or no evidence of cirrhosis.[1] The risk for progression to cirrhosis and liver failure in these patients is minimal. NASH is defined by the presence of hepatic steatosis and inflammation with hepatocyte injury (ballooning) with or without cirrhosis.[1] NASH can progress to cirrhosis, liver failure and occasionally liver cancer.

NAFLD is now considered to be the commonest cause of chronic liver disease in developed countries with as high as 30% of the general population affected.[2, 4] In newly identified cases of chronic liver disease in a US survey, 39% had NAFLD.[2] A high prevalence of NASH among NAFLD cases has been reported[2]: up to 55% in patients with elevated aminotransferases[5, 6], as high as 49% in morbidly obese patients[7, 8], and 67% in a subset of patients with incident chronic liver disease.[9]

Half a billion adults worldwide are estimated to be obese and 1.5 billion are overweight or obese.[10, 11] Overall, about two-thirds of the population in the developed world have a BMI greater than 25 kg/m^2.[12] Primary NAFLD/NASH is associated with insulin resistance (IR) and its phenotypic manifestations. There are clear relationships between NAFLD and obesity[13] and between NAFLD and diabetes independent of obesity.[14] Systemic IR is considered to be the key risk factor for development of NAFLD.[15] The close relationship between NAFLD/NASH and type 2 diabetes mellitus (DM) leads to overlapping risk and complications and attendant economic burden for health care systems.

Despite the high prevalence of NAFLD, no safe and effective treatment is currently available.[16] Management strategies for NAFLD/NASH rely primarily on non-pharmacologic measures. Since patients with NAFLD without steatohepatitis have excellent prognoses from a liver standpoint, treatments aimed at improving liver disease should be limited to those with NASH.[1]

Life-style modifications are effective but adherence is difficult to maintain.[17] Bariatric surgery can be performed in selective obese patients, but is too drastic to be the treatment of choice and thus it is not recommended for treating NASH.[18] Vitamin E has been effective in treating nondiabetic NASH patients without cirrhosis.[19] The long-term safety and efficacy of pioglitazone are not clear in NASH.[20, 21] Metformin[22], ursodeoxycholic acid, omega 3 fatty acids, and statins are not considered as therapy for NAFLD/NASH patients.[1, 21]

TYPE 2 DIABETES and NAFLD/NASH

Type 2 DM involves failure of the action and utilization of insulin within the body. Type 2 sufferers have an endogenous resistance to insulin. The disease appears when they fail to manufacture sufficient insulin levels to overcome this resistance. This relative lack of insulin eventually leads to chronic hyperglycemia.

Traditionally, type 2 was known as "adult-onset diabetes" (with type 1 being referred to as "juvenile-onset" diabetes) as it generally struck adults, usually overweight, of age 45 and over. However, in recent years, the incidence of type 2 DM has skyrocketed—to the extent that it is now being termed a global "pandemic." Type 2 DM is strongly correlated with obesity, and so this disproportionate increase is considered a reflection of the twin ills of modern life—overeating/obesity and decreased physical activity.

The 2014 CDC National Diabetes Statistics Report estimated that 29.1 million people or 9.3% of the US population have diabetes; 21 million diagnosed and 8.1 million undiagnosed.[23] Another 86 million (37% of US adults aged 20 years and older) people were estimated to suffer from pre-diabetes, a condition that increases the risk of developing type 2 DM—the more common form of the disease—as well as heart disease and stroke.

Comparable statistics may be found in both developed and developing countries around the world as the frequency of diabetes continues to rise. Global prevalence of diabetes is now estimated at more than 380 million, or about 8% of the worldwide adult population according to the International Diabetes Federation. Type 2 DM represents 85-95% of both present and future cases.[24]

As noted above, the prevalence of NAFLD can be as high as 90–95% in obese individuals and up to 70% of patients with type 2 DM develop NAFLD.[25] In addition, they share similarities in their risk factors, pathogenic mechanisms and complications.

INSULIN TREATMENT

There is no known cure for diabetes. Treatment of the disease requires constant care and monitoring, along with some form of insulin or drug therapy coupled with diet and exercise.

Patients with type 2 DM have generally been prescribed a diet and exercise program as well as oral medication in order to control blood glucose levels. However, diet and oral hyperglycemic agents have failed to provide a satisfactory control of type 2 DM in a progressively larger proportion of these patients. Therefore, there is now an increasing trend to treat type 2 diabetic patients with insulin as well, in order to avoid the potential complications from hyperglycemia.

New Approaches To Insulin Therapy

In the past decade, several major studies (DCCT, UKPDS and others) have focused attention on the need for strict control of glycemia to prevent and/or reduce the risk of both the specific microvascular and the less specific macrovascular complications.[26,27] The mounting numbers of type 2 sufferers worldwide, coupled with the growing tendency to treat this form of diabetes with insulin therapy, means that there are currently millions of individuals, adults as well as children, who must inject themselves several times each day throughout their entire lives. Injections are painful, inconvenient, and frightening for many patients. Over time reluctance to carry out injections increases and many patients become non-adherent to therapy.

In addition, the subcutaneous administration of insulin does not provide, in most cases, the fine continuous metabolic regulation that occurs normally with insulin secreted from the pancreas directly into the liver via the portal vein.

An ideal solution for treating these diabetics would be to transplant healthy insulin producing cells (pancreatic islets) into the patient. However, direct transplantation has not yet been practical. The immune system of the recipient recognizes the cells as foreign and rejects them. The side effects of drugs necessary to suppress the immune system are too severe to justify their use in otherwise healthy patients.

Consequently, research is underway to develop a new and different approach that would both improve the administration of insulin and provide a way by which the hormone can reach the liver in a physiological manner, namely, oral administration of insulin.

ORAL ADMINISTRATION OF INSULIN

Insulin injections are, intrinsically unpleasant and patients may cease to perform them, leading to a multitude of possible complications. In addition, subcutaneous injection is not the most physiologically efficient mode of insulin transfer to the body. Hence, the search for an oral form of insulin has been underway since Banting and Best's discovery of insulin in 1922. Oral insulin would free patients of the pain and inconvenience of injections while providing a more physiologically advantageous route of administration.

Proposed Mechanism

Any attempt to develop an oral insulin modality must take into account two major obstacles that result from insulin's biochemical characteristics as a polypeptide: 1) Its direct transfer across the mucosal barrier is restricted; 2) it is subject to degradation by the proteolytic enzymes located in the stomach and intestinal lumen.

To overcome these barriers, Oramed has proposed a mechanism to prevent the digestion of the introduced hormone in the gastrointestinal tract and to facilitate its physiological absorption. After performance of a range of studies for optimization of co-factors to

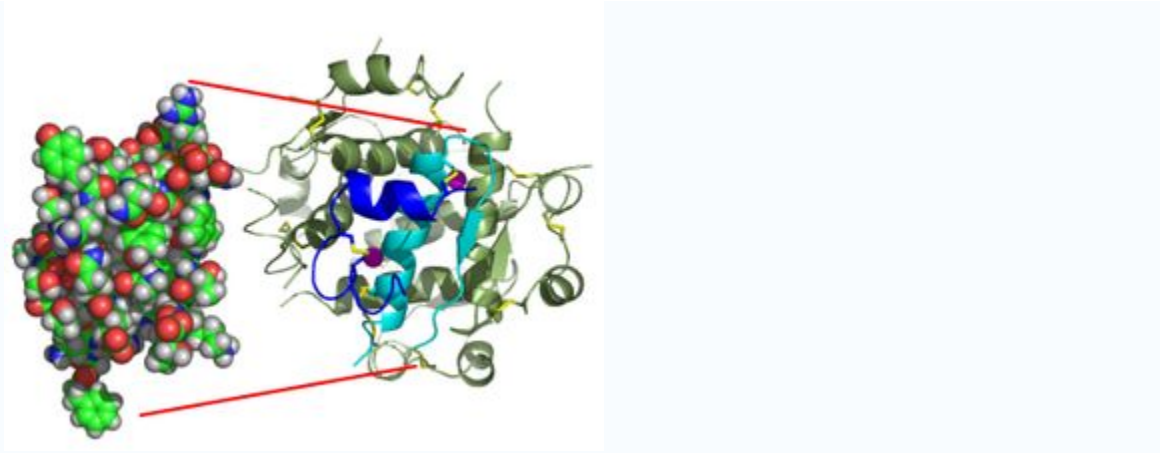
prevent the digestion of insulin, Oramed has identified the most efficacious formulation of encapsulated oral insulin. The proposed composition contains: (1) crystalline insulin, (2) EDTA as enhancer, (3) soybean trypsin (SBTI), and (4) omega 3-rich fish oil, in a coated capsule. These components are expanded upon in greater detail below. Each has a target function, which promotes the goals of our treatment modality. The chelating agent EDTA functions as an effective enhancer of the mixture. The SBTI prevents enzymatic degradation of the insulin by mucosal enzymes.

Modality Components

Insulin:

Structure:

Insulin is a polypeptide hormone produced by cells in the islets of Langerhans in the pancreas. Human insulin consists of two different peptide chains, the A (acidic) chain of 21 amino acids and the B (basic) chain of 30 amino acids, connected by two disulfide bridges. The A chain contains a third disulfide bond.



The structure of insulin: The left hand side of the panel is a space-filling model of the insulin monomer, believed to be biologically active. Carbon is green, hydrogen white, oxygen red, and nitrogen blue. On the right hand side is a cartoon of the hexamer, believed to be the stored form. A monomer unit is highlighted with the A chain blue and the B chain cyan. Yellows denote disulfide bonds, and magenta spheres are zinc ions.
Source: Created by Isaac Yonemoto. Created with Pymol, Inkscape, and Gimp from NMR structure 1ai0 in the pdb. Ref: Chang, X., Jorgensen, A.M., Bardrum, P., Led, J.J.

ORAL INSULIN FOR NAFLD/NASH

The similarities between type 2 DM and NAFLD/NASH in risk factors, pathogenic mechanisms and complications suggest common approaches to therapeutic intervention. Recall that 70% of type 2 DM patients will develop NAFLD/NASH and that 85% of new cases of diabetes will be type 2 patients. The key component of insulin resistance shared by diabetes and NAFLD/NASH makes direct insulin intervention an attractive option. The oral insulin formulation has the potential advantage of first pass metabolism in the liver allowing local availability and concentration of insulin at the affected liver fat cells.

ORAL INSULIN DEMONSTRATIONS OF EFFICACY IN TYPE 2 DIABETES

Oramed's research and development team has performed multiple studies on pigs and canines over the last decade. The studies were designed to optimize the composition and functionality of our oral insulin modality and to demonstrate its safety and efficacy for use in animals and humans. The completed studies in humans are briefly described in **Appendix A**.

ORA-H-N01 NASH STUDY DESIGN

This is an open, pilot study using the oral ORMD-0801 insulin formulation in patients with NASH and confirmed type 2 DM. The study will consist of a Screening, Placebo run-in, Treatment Phase and End-of-Study Phase.

STUDY OBJECTVIES

Primary Objective

- To evaluate the safety of oral insulin in patients with nonalcoholic steatohepatitis (NASH) and type 2 DM.

Secondary Objective

- To assess whether oral insulin may be effective in reducing liver fat content and inflammation in patients with NASH and type 2 DM.

Study Duration

Screening Phase: up to 14 days prior to placebo run-in period
Placebo run-in Phase: 2 weeks
Treatment Phase: 12 weeks
End-of-Study (EOS): After completion of 4 weeks after end of treatment

Study Population and Size

This exploratory study will first enroll 10 patients with NASH and type 2 DM.
At the completion of their 4-week follow-up period, results will be presented to the Helsinki Committe. Following approval, an additional 20 patients will be enrolled. The size of the study population was determined by the investigator (with literature review) to be sufficient to show trends of reducing liver fat content by MRI PDFF (MRI-Proton Density Fat Fraction) images, the FibroMax Test and Fibroscan including CAP.

Inclusion Criteria:

1. Male or female aged 18-70 years.
2. BMI ≥25
3. Known type 2 DM according to American Diabetic Association (one of the three needed): Fasting Plasma Glucose ≥126 mg/dl or 2h postprandial (PG) following 75g OGTT ≥200 mg/dl or HbA1C > 5.7%[28] or on treatment with metformin
4. Abdominal ultrasound (US) proven fatty liver performed within 6 months before randomization.
5. Fat concentration in the liver of S2 (moderate steatosis, 6–32% hepatocytes with steatosis) or more as measured by Fibromax (SteatoTest and NASHTest Components, BioPredictive, Paris, France[29]).[1] Or MRI PDFF >10%.
6. Liver enzyme abnormalities: Up to 5 times ULN.
7. Evidence of ≥stage 3 fibrosis, as determined by FibroScan
8. Signature of the written informed consent.
9. Negative pregnancy test at study entry for females of child bearing potential.
10. Females must have a negative urine pregnancy test result at screening, prior to the start of the run-in period, and at initiation of active dosing. A negative urine and serum pregnancy test must be obtained prior to active dosing. Males and females of childbearing potential must use two methods of contraception (double barrier method), one of which must be an acceptable barrier method from the time of screening to the last study visit (12 weeks). Barrier methods of contraception include male condoms plus spermicide, diaphragm with spermicide plus male condom, cap with spermicide plus male condom, or oral contraceptives. Acceptable methods of birth control include abstinence, oral contraceptives, surgical sterilization, vasectomy, the contraceptive patch, and the contraceptive ring. If a subject is not usually sexually active but becomes active, he or his partner should use medically accepted forms of contraception. Sperm donations will not be allowed for the duration of the study and for 90 days after the last dose of study drug.
    Females of non-childbearing potential are defined as postmenopausal who a) had more than 24 months since last menstrual cycle with menopausal levels of FSH, b) who are surgically menopausal (surgical sterility defined by tubal occlusion, bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
11. For hypertensive patients, hypertension must be controlled by stable dose of anti-hypertensive medication for at least 2 months prior to screening (and the stable dose can be maintained throughout the study) with BP < 150/<95 mmHg
12. Patients previously treated with vitamin E (>400IU/day), Polyunsaturated fatty acid (>2g/day) or Ursodeoxycholic acid fish oil can be included if drugs are stopped at least 3 months prior to diagnostic liver biopsy and up to the end of the study.
13. Glycaemia must be controlled (Glycosylated Hemoglobin $A1_C$ ≤8.5%) while any $HbA1_C$ increment should not exceed 1% during 6 months prior to enrolment).

[1] FibroMax consists of algorithms based on results from the following set of biochemical tests: alpha-2 macroglobulin, haptoglobin, apolipoprotein A1, total bilirubin, ALT, AST, GGT, fasting glucose, triglycerides and total cholesterol. See Poynard, et al., 2005 for discussion of diagnostic value.

Exclusion Criteria

1. Patients with active (acute or chronic) liver disease other than NASH (e.g. viral hepatitis, genetic hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency, alcohol liver disease, drug induced liver disease) at the time of randomization.
2. ALT or AST > 5 times ULN
3. Abnormal synthetic liver function (serum albumin ≤3.5gm%, INR >1.3).
4. Known alcohol and/or any other drug abuse or dependence in the last five years.
5. Weight >120 Kg
6. Known history or presence of clinically significant, cardiovascular, gastrointestinal, metabolic (other than diabetes mellitus), neurologic, pulmonary, endocrine, psychiatric, neoplastic disorder or nephrotic syndrome.
7. History or presence of any disease or condition known to interfere with the absorption, distribution, metabolism or excretion of drugs including bile salt metabolites (e.g. inflammatory bowel disease (IBD), previous intestinal (ileal or colonic) operation, chronic pancreatitis, celiac disease or previous vagotomy.
8. Weight loss of more than 5% within 6 months prior to randomization.
9. History of bariatric surgery.
10. Uncontrolled blood pressure BP ≥150/≥95.
11. Non type 2 DM (type 1, endocrinopathy, genetic syndromes etc).
12. Patients with HIV.
13. Daily alcohol intake >20 g/day for women and >30 g/day for men.
14. Treatment with anti-diabetic medications other than metformin, such as sulfonylurea, DPP-4 inhibitors, GLP-1 receptor agonists, TZDs, etc.
15. Metformin, fibrates, statins, not provided on a stable dose in the last 6 months.
16. Patients who are treated with valproic acid, Tamoxifen, methotrexate, amiodarone.
17. Chronic treatment with antibiotics (e.g. Rifaximin).
18. Homeopathic and/or Alternative treatments. Any treatment must be stopped before the screening period.
19. Uncontrolled hypothyroidism defined as Thyroid Stimulating Hormone >2X the upper limit of normal (UNLN). Thyroid dysfunction controlled for at least 6 months prior to screening is permitted.
20. Patients with renal dysfunction: eGFR< 40 ml/min.
21. Unexplained serum creatinine phosphokinase (CPK) >3X the upper limit of normal (UNL). Patients with a reason for CPK elevation may have the measurement repeated prior to randomization; a CPK retest > 3X ULN leads to exclusion.

STUDY PERIODS

The following parameters will be measured and recorded taken at each of the visits, as specified below:

Screening Phase

Screening process will take place at Visit 1, up to 14 days prior to placebo run in treatment.

Visit 1 (up to week -4)

- Medical history
- Medication history
- Complete Physical examination (PE)
- ECG
- Vital signs (blood pressure, heart rate). Vital signs will be measured in the sitting position after at least 5 minutes of rest.
- Clinical laboratory evaluations
    - Chemistry: Electrolytes, BUN, creatinine, glucose level, liver function tests (LFT) including transaminases (ALT, AST), albumin, and alkaline phosphatases, creatine phosphokinase (CPK)
    - Hematology: Complete blood count (CBC)

Run-in Phase (to week -2)

The run-in phase will consist of 2 weeks period starting at visit (Visit 2) week -2

Visit 2

- Informed consent
- Medication history
- Brief physical examination
- Treatment (run in placebo)
- Vital Signs
- Self-monitored fasting morning blood glucose (finger-stick) of fasting blood glucose will be recorded in the patient diaries 3 days weekly in the morning.

Treatment Phase (week 0)

The Treatment Phase will consist of a treatment period of 12 weeks that will start at visit 3 (week 0) and outpatient visits at week 1, 2, 4, 8, and 12 (final visit).
At each visit patients will have

- Medication history
- Brief Physical examination (PE)- at Visits 4,5, 6, and 7
- Treatment
- Medication Compliance
- Vital signs (blood pressure, heart rate). Vital signs will be measured in the sitting position after at least 5 minutes of rest.

At Visits 3 (baseline), 6, 7, and 8, patients will have

- Clinical laboratory evaluations (chemistry, hematology)
- Fasting blood glucose and insulin (also used for HOMA estimates)[2]
- Self-monitored fasting morning blood glucose (finger-stick) of fasting blood glucose will be recorded in the patient diaries 3 days weekly in the morning.
- Adiponectin

At Visits 3 and 8 Patients will have

- Complete PE
- FibroMax Test
- Fibroscan
- MRI PDFF

End-of-Study (EOS) (week 16) /Early Discontinuations

The EOS visit (Visit 9) will be conducted 4 weeks following the last scheduled treatment visit. Patients will complete the following EOS evaluations:

- Medication history
- Complete PE, only if the investigator deems it necessary.
- EOS ECG, only if the investigator deems it necessary.
- Vital signs (blood pressure, heart rate) will be measured in the sitting position after at least 5 minutes of rest, only if the investigator deems it necessary.
- Clinical laboratory evaluations (chemistry, hematology)
- Fasting blood glucose
- Fasting blood Insulin
- Adiponectin

Patients who are discontinued early from the study will complete the EOS evaluations at the time of early discontinuation.

Unscheduled visit

The patient may be required to return for an unscheduled visit for a repeat measurement of fasting blood glucose, if the investigator deems it necessary.

[2] HOMA = The Homeostasis Model Assessment

Self-Monitoring Fasting Blood Glucose and Patient Diaries

All patients will self-monitor fasting morning blood glucose levels three (3) times weekly during the run-in and treatment period. Monitoring must be performed at the same time each designated day (± 10 minutes) prior any caloric intake. Patients will be required to record the values in a patient diary and bring the diary to each clinic visit; Information recorded for the fasting blood glucose will be reviewed by the clinical research coordinator for completeness and transcribed onto CRF's. During the study, both fasting finger stick glucose and laboratory fasting plasma glucose will be obtained.

If a fasting blood glucose measures greater than or equal to 270 mg/dL (15 mmol/L) during daily self-monitoring or during any in-clinic visit, the patient will be required to contact the clinic to report the value. Blood will be drawn and sent to lab for plasma glucose determination. The patient may be required to return for an unscheduled visit to the clinic for a repeat measurement of fasting blood glucose within one week after the original measurement. If the repeat measurement is also greater than or equal to 270 mg/dL, the patient will be discontinued from treatment with study drug and offered rescue medication. The patient will continue to be seen for all remaining study visits, if possible.

Fingerstick glucose values of <50 mg/dL (2.78 mmol/L) should be confirmed by laboratory plasma glucose measurements and if three or more are observed within 12 hours subsequent to administration of study drug without a reasonable explanation (such as increased physical activity and/or skipped meal), the patient will be discontinued from treatment with study drug and rescued with glucose administration (20g of glucose tablets) which will be available at all times at the study site. This information will be recorded in the patient's diary and the patient will be instructed to contact the study site if this occurs. The patient will continue to be seen for all remaining study visits.
Sites will instruct patients to immediately perform a finger stick glucose measurement if any symptoms occur that may be related to hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), and to avoid delay in treating these symptoms. The measurements will be recorded in the patient diary. Patients will always carry glucose tablets with them and ingests 3-4 tablets if hypoglycemia occurs.

Hypoglycemia and associated symptoms (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), have been associated with insulin administration, including ORMD-0801.

Table 1: Schedule of Assessments

Assessments	Screening	Placebo	Treatment						Un Scheduled Visit	End-of-Study / Early Termination
Week	**up to -4**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**Not Defined**	**16**
Days	**Up to -28**	**-14**	**7± 2**	**7± 2**	**14± 2**	**28± 2**	**56± 2**	**84± 2**		**112±2**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Un Scheduled**	**9**
Written informed consent	X									
Medical history	X									
Medication history	X	X	X	X	X	X	X	X		X
Complete physical examination	X		X					X		(X[1])
~~Brief physical examination~~		~~X~~	~~X~~	~~X~~	~~X~~	~~X~~	~~X~~			
Treatment		X	X	X	X	X	X			
Medication compliance check			X	X	X	X	X	X		
ECG	X									(X[1])
Vital signs	X	X	X	X	X	X	X	X		(X[1])
Clinical laboratory evaluations[2]	X		X			X	X	X	(X[1])	X
~~Fasting blood glucose~~[3]		X	X			X	X	X	(X[1])	X
Fasting Insulin[3]		X	X			X	X	X		X
Self-monitored fasting morning blood glucose[4]		X	X	X	X	X	X	X		
Adiponectin			X			X	X	X		X
FibroMax Test			X					X		
Fibroscan Test			X					X		
MRI PDFF			X					X		

[1]Only if investigator deems necessary
[2]Chemistry (electrolytes, BUN, creatinine, glucose, LFTs) and CBC
[3]Fasting blood ~~glucose and~~ insulin will be used to determine HOMA estimates.
[4]Self-monitoring (finger-stick) of fasting blood glucose will required 3 days weekly in the morning and recorded in patient diaries.

TREATMENT REGIMEN

The treatment regimen will consist of a soft gelatin capsule containing 8 mg insulin, and 75 mg SBTI. Patients will take 2 capsules daily in the morning with or without food.

SAFETY EVALUATIONS

See complete instructions about Safety and Adverse Events evaluation and reporting in **Appendix B**.

- Adverse events will be collected throughout the study beginning from the time the patient signs the consent form until the EOS evaluations
- Concomitant medications/therapies will be recorded throughout the duration of study, beginning from the time the patient signs the informed consent.
- Vital signs (blood pressure, heart rate) will be measured in the sitting position after at least 5 minutes of rest at all visits
- Clinical laboratory evaluations (chemistry, hematology) will be performed at screening and at weeks 0, 4, 8, 12, and 16.
- Treatment of significant hyperglycemia, will be tailored to the medical history and needs of the patient, as per recommended treatment guidelines.
- Symptomatic hypoglycemia - Hypoglycemia as noted by a feeling of hypoglycaemia with concomitant blood glucose measurements below 70.
    - All occurrences of hypoglycemia will be treated with orange juice, 3-4 glucose tablets, or a 20% glucose solution via an I.V. bolus injection over 1 to 2 minutes and the subject will be monitored until symptoms have resolved.
    - If three or more finger stick glucose values of <50 mg/dL (2.78 mmol/L) are observed in one week within 12 hours subsequent to administration of study drug without a reasonable explanation (such as increased physical activity and/or skipped meal), the patient will be discontinued from treatment with study drug. This information will be recorded in the patient's diary and the patient will be instructed to contact the study site if this occurs. The patient will continue to be seen for all remaining study visits.
    - The site will instruct patients to immediately perform a finger stick glucose measurement if any symptoms occur that may be related to hypoglycemia (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), and to avoid delay in treating these symptoms. The measurements will be recorded in the patient diary.
    - Patients will always carry glucose tablets with them and ingests 3-4 tablets if hypoglycemia necessitates it.

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APPENDIX A: Studies of Oramed Oral Insulin in Humans

Phase 1A Clinical Trial

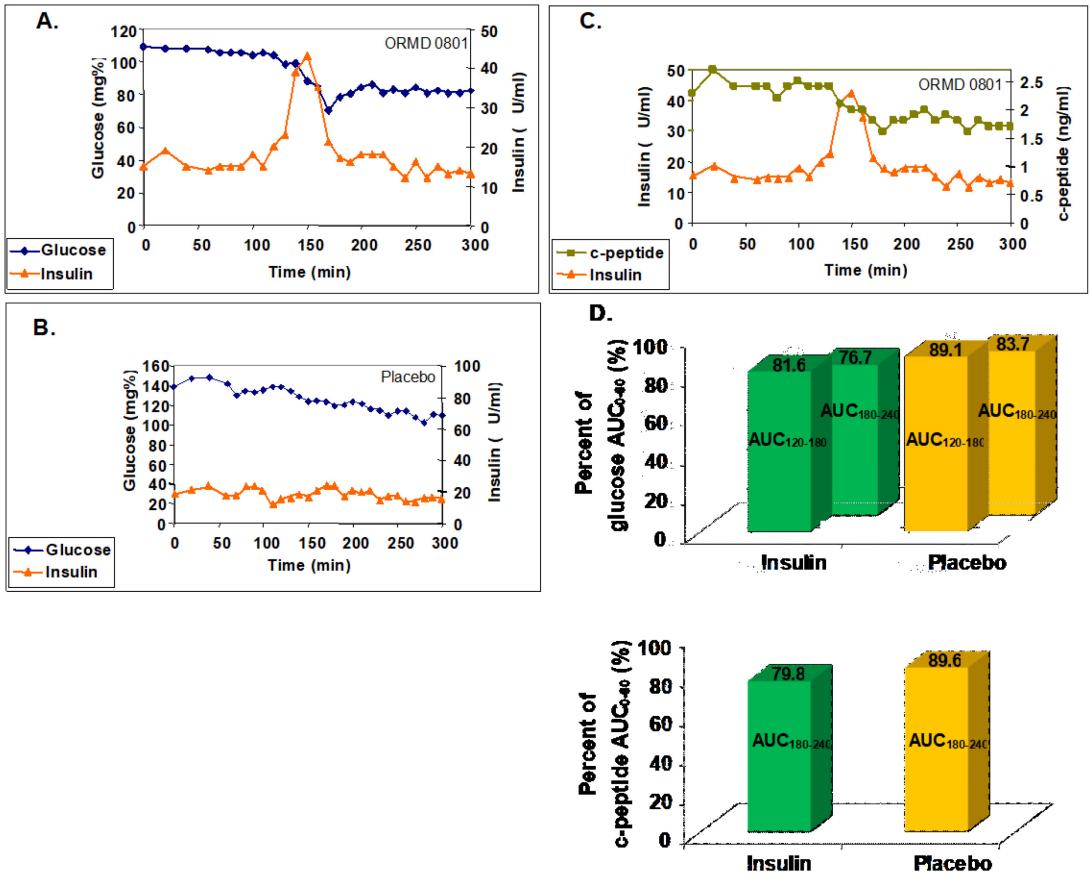
The encouraging outcome of the pre-clinical studies set the stage for Phase 1a clinical trials that evaluated oral insulin on eight healthy male volunteers during four separate visits. The study was completed in August of 2007. The results of this study clearly demonstrated that the insulin administered by Oramed's capsules was absorbed and retained its biologically activity. Additionally, it exhibits unique PK and PD effects characterized by the delayed onset of action and a prolonged metabolic effect as compared with other oral or inhaled formulations currently under study.

Phase 1B Clinical Trial

Oramed then continued with a formulation optimization (Phase 1b) clinical trial which included eight healthy male volunteers studied during five visits. The trials were completed in March of 2008 and the results showed again that insulin combined with Oramed's drug delivery enhancers and formulated in a capsule dosage form was absorbed and resulted in plasma glucose reduction, a decrease in c-peptide and an increase in insulin. A lead formulation was identified as a result of this study.

Phase 2A– Type 2 Diabetes Mellitus Clinical Trial

In August 2008, Oramed completed Phase 2a clinical trials of ORMD 0801. The trial included ten Type 2 diabetic patients studied over the course of seven visits. The goal of these trials was to evaluate the safety and efficacy of oral insulin on patients with diabetes. The results of this clinical trial showed that Oramed's oral insulin capsule can effectively deliver insulin to people with diabetes and result in lowering blood glucose levels. Furthermore oral insulin (ORMD 0801) was found safe and was well tolerated.



Figures A-D: **A.** Representative glucose and insulin recordings of an ORMD 0801 responder over the 5hrs of testing. **B.** Representative glucose and insulin recordings of a placebo-treated subject over the 5 hrs of testing. **C.** Representative c-peptide and insulin recordings of an ORMD 0801 responder. **D.** AUC120-180 and AUC180-240 calculations presented as ratios of AUC0-60 of both glucose and c-peptide levels following ORMD 0801 and placebo treatments.

Phase 2A– Type 1 Diabetes Mellitus – Clinical Trial

Oramed then proceeded with a Phase 2A clinical trial assessing the safety, tolerability and food effect study of ORMD-0801, in patients with type 1 diabetes. ORMD-0801 was well tolerated by patients with Type 1 diabetes mellitus and no adverse events were encountered during the study. The insulin absorption was not perturbed when given shortly (10 minutes) before meal ingestion.

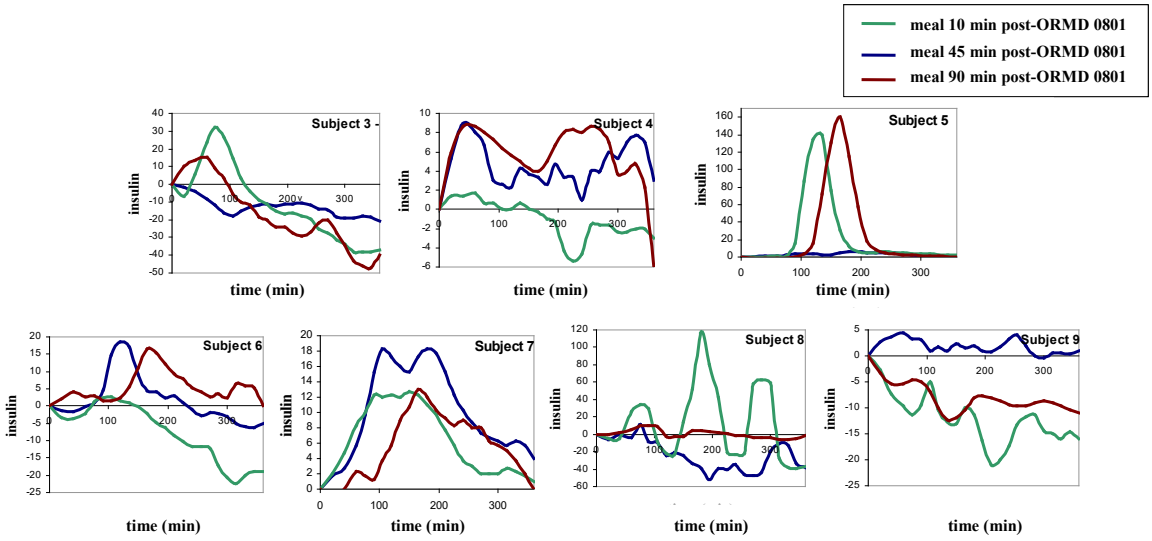


Figure 1. ORMD 0801 levels after administration of two single-dose capsules: Subjects were administered two capsules of a specific ORMD 0801 formulation at three independent treatment sessions. Meals were served either 10, 45 or 90 minutes post-administration. Blood samples were drawn throughout the monitoring sessions and insulin levels were measured. Moving averages of normalized insulin recordings were graphed as a function of time.

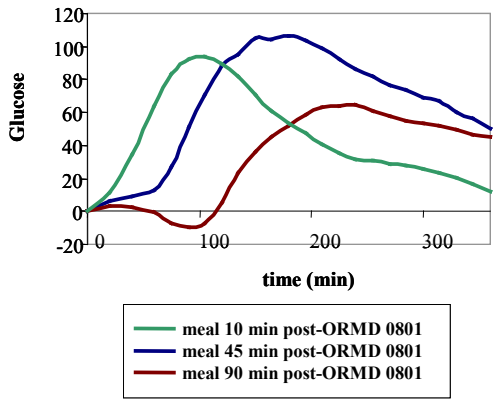


Figure 2. Averaged normalized glucose readings for all seven subjects: Two glucose recordings were obtained for each subject at each blood sample drawing. An average was calculated and moving averages were determined for each individual subject for each treatment session. An average of the moving averages of all seven subjects was then computed and graphed as glucose readings as a function of time.

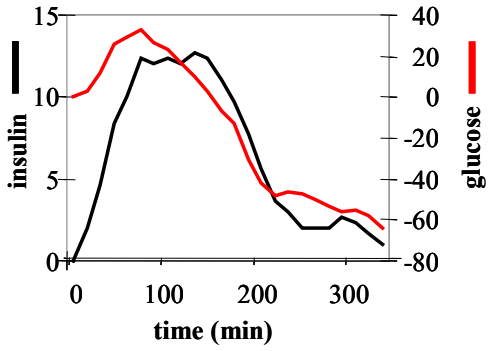


Figure 3. Classic influential relationship of insulin on post-meal glucose levels: Moving averages of insulin and glucose levels of subject #7 were co-plotted to illustrate the temporal relationship between the insulin peak and glucose rise and decline post-meal served 10 minutes after drug administration

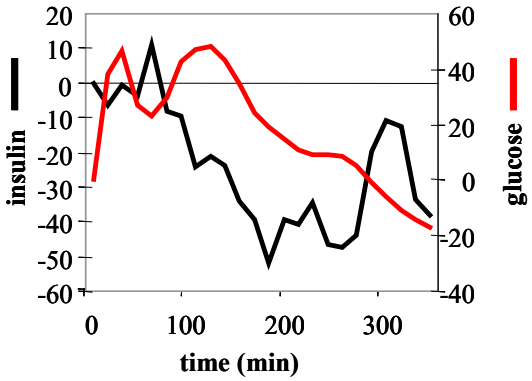


Figure 4. Slight plasma insulin peaks suffice for post-meal glucose concentration regulation: Moving averages of insulin and glucose levels of subject #8 were co-plotted to illustrate the temporal relationship between the insulin peak and glucose rise and decline post-meal served 45 minutes after drug administration

In contrast, subjects with undetectable insulin levels following ORMD 0801 administration, demonstrated elevation of blood sugar concentrations following food consumption, with slow or no (Figure 5) significant decrease within the 360 minute monitoring session.

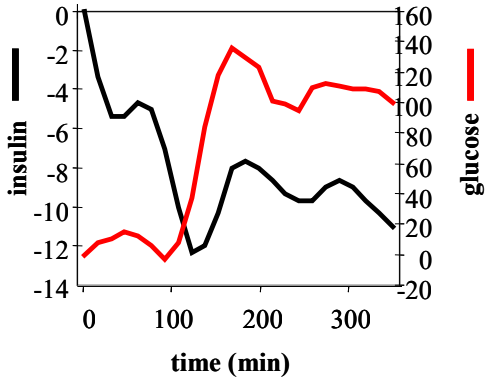


Figure 5. Glucose levels follwoing undetectable insulin peaks: Moving averages of insulin and glucose levels of subject #9 were co-plotted to illustrate the lack of decline in postmeal glucose concentrations despite drug administration.

Phase IIb – Type 2 Diabetes Mellitus - Clinical Trial

This multi-site, placebo-controlled, randomized, double-blinded study, conducted in South Africa, focused on the responses of 29 Type II diabetes (T2DM) patients to ORMD-0801. Volunteers received a once-daily, fixed dose of oral insulin capsules (8 mg/capsule, 2 capsules = 16 mg/day) for a period of six weeks. Three of the subjects were otherwise on diet, while 27 were on diet+Metformin (≥ 2.5 g/day) diabetes management programs before the study. The primary objective of this trial was to assess the safety and tolerability of the investigational product, by monitoring adverse events, hypoglycemia and other safety parameters throughout the study. Secondary endpoints evaluated the effectiveness of ORMD-0801 in providing glycemic control, as determined by comparison of baseline fasting blood glucose (FBG), insulin, fructosamine, c-peptide, C-reactive protein (CRP) and Hb1Ac levels to those measured after the 6-week treatment period.

The 6-week ORMD-0801 treatment regimen proved safe and tolerable, with no reports of serious AEs throughout the study period. No cumulative effects of extended exposure to

ORMD-0801 were observed, and only two mild hypoglycemic events were recorded in patient diaries (Table 1).

Table 1: Adverse Events ORMD-0801 Cohort*

Event	Severity	Action	Outcome	Notes
Hypoglycaemia	Mild	Dose not changed	Recovered	Blood sugar: 12.0 mmol/L
Hypoglycaemia	Unknown	Unknown	Unknown	Hypoglycaemic on clinical symptoms
Constipation	Mild	Dose not changed	Not recovered	
Diarrhoea and skin rash	Mild	Dose not changed	Recovered	
Diarrhoea	Mild	Dose not changed	Recovered	
Increased bowel movement	Mild	Not applicable	Recovered	

* no AEs were reported in the placebo cohort

Efficacy evaluations were performed on blood samples of 21 patients on oral insulin and 8 patients on placebo. Mean decreases in insulin and CRP levels were found to be statistically significant following the 6-week, once-daily ORMD-0801 treatment period, when compared to the placebo group (Figure 6A). These findings suggest that ORMD-0801 offered temporary relief to insulin-secreting beta cells. Moreover, the percentage of subjects demonstrating clinically relevant reductions in insulin, c-peptide, FBG and Hb1Ac levels was always higher in the ORMD-0801 cohort, when compared to the placebo (Figure 6B).

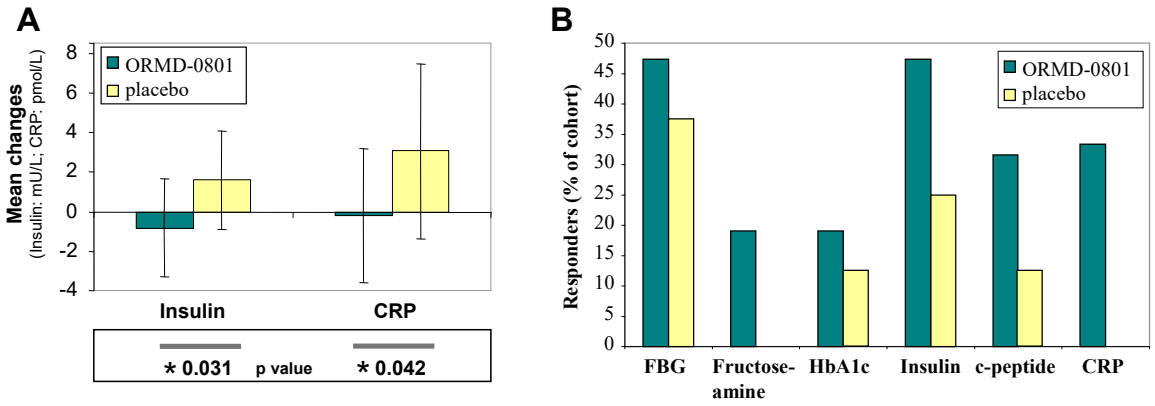


Figure 6. Plasma marker responses and percent responders to a six-week, daily oral ORMD-0801 regimen T2DM patients were treated once daily with a 16 mg insulin ORMD-0801 formulation or placebo capsule. Blood samples drawn at the start of the study and after a 6-week treatment period were tested for marker levels. A. Mean changes (±SD) in plasma insulin and CRP levels between the samples of day 0 and samples taken after the 6-wk treatment period are presented. B. Subjects demonstrating a decrease of ≥0.5 mmol/L in FBG, ≥40 µmol/L fructose-amine, ≥0.6% Hb1Ac, ≥1 mU/L insulin, ≥100 pmol/L c-peptide or ≥1 mg/L CRP were considered responders for that specific marker. The number of responders for each tested marker is presented as the percent of the total number of subjects analyzed for the given parameter.

Further investigation involving univariate, covariate and multivariate analyses, demonstrated positive correlations between above-average recordings of subject baseline triglyceride, BMI, insulin, HbA1c, c-peptide or blood pressure and/or below borderline-high levels of baseline cholesterol or LDL, and increased CRP responses (Table 2). When only considering individuals presenting these predictors (72.4-75.9% of the original study population), more significant decreases in CRP levels than those obtained for the full intent-to-treat (ITT) population, were observed following insulin-based treatment, when compared to placebo. In these cases, mean intercohort differences in CRP levels ranged between 73.9-87.6% (p-values: 0.022-0.007), demonstrating a strong impact of the oral insulin preparation on inflammatory response with expected influence on insulin sensitivity.

Table 2. Clinically relevant predictors for heightened CRP responses among T2DM patients											
	Predictor	**ORMD-0801 (N)**	**Placebo (N)**	**Percent of ITT population (%)**	**Mean change ORMD-0801**	**Mean change placebo**	**SD change ORMD-0801**	**SD change placebo**	**Difference between cohorts using the optimal rule (%)**	**p-Value Under Optimal Rule**	**Adjusted p-Value Optimal Rule**
1	0.86 <= BASELINE_TRI <= 3.11	13	8	72.4	-1.3385	3.05	2.032	3.1625	-73.90%	0.0138	0.0036
2	7.5 <= BASELINE_HBA1C <= 10.1	16	7	79.3	-0.9875	3.5571	2.3984	3.1796	-76.50%	0.014	0.0056
3	27.1 <= VS_BMI	15	7	75.9	-1.0533	3.5571	2.4969	3.1796	-77.60%	0.0153	0.0052
4	BASELINE_CHOLESTEROL <= 6.15	17	5	75.9	-0.4647	4.54	2.2803	3.408	-84.30%	0.0159	0.0054
5	1.39 <= BASELINE_LDL <= 4.17	16	5	72.4	-0.3125	4.54	2.2516	3.408	-81.70%	0.0217	0.0067
6	123 <= VS_BP_SYS	16	6	75.9	-0.3438	4.1167	1.8812	3.15	-75.10%	0.0076	0.0021
7	123 <= VS_BP_SYS AND BASELINE_HDL <= 1.73	16	5	72.4	-0.3438	4.86	1.8812	3.152	-87.60%	0.0038	0.0006
8	123 <= VS_BP_SYS AND 493 <= BASELINE_CPEP	15	6	72.4	-0.5333	4.1167	1.8089	3.15	-78.30%	0.0065	0.0013
9	123 <= VS_BP_SYS AND BASELINE_HDL <= 1.73	16	5	72.4	-0.3438	4.86	1.8812	3.152	-87.60%	0.0038	0.0006
10	123 <= VS_BP_SYS AND 6.4 <= BASELINE_INSULIN	16	5	72.4	-0.3438	4.86	1.8812	3.152	-87.60%	0.0038	0.0006
11	123 <= VS_BP_SYS AND 493 <= BASELINE_CPEP	15	6	72.4	-0.5333	4.1167	1.8089	3.15	-78.30%	0.0065	0.0013
12	7.5 <= BASELINE_HBA1C <= 10.1 AND 30 <= AGE	15	7	75.9	-1.3733	3.5571	2.1982	3.1796	-83.00%	0.0071	0.0019
13	123 <= VS_BP_SYS AND 1 YR <= METFORMIN_DURATION	16	5	72.4	-0.3438	4.54	1.8812	3.408	-82.20%	0.0073	0.0015

The reported results substantiate the safety and tolerability of ORMD-0801 and demonstrate a relevant clinical impact of ORMD-0801 at the tested dose. The small sample size and placebo effect, thoroughly described in the literature for diabetes management studies, contributed to the often nonsignificant outcomes in baseline vs. post-treatment marker levels. However, this first analysis of long-term exposure to ORMD-0801, proved its safety and tolerability, and will lay the foundation for further testing in larger populations. In addition, the findings related to CRP responses present factors which may be essential in further understanding interpatient insulin response variability, which to date, has challenged healthcare providers in outlining effective glucose control protocols. Definition of highly responsive subject subpopulations is expected to enhance insulin-based treatment efficacy.

APPENDIX B: Adverse Event Reporting

Adverse Events

Information about all adverse events, whether volunteered by the patient, recorded in the patient's diary, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the Adverse Event Case Report Form and followed-up as appropriate.
Medical conditions present at study entry are considered pre-existing conditions and will be documented as medical history in the study source and CRF documents. All adverse events, including worsening of pre-existing conditions, must be reported and documented as described below.

Definitions
An adverse event is any untoward medical event that occurs in a patient or patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Assessment of Adverse Events
Volunteered, observed, and elicited reports of adverse events must be recorded. This includes adverse events the patient reports spontaneously, those the Investigator observes, and those the study staff elicits in response to open-ended questions during study visits. Each adverse event will be assessed by the Investigator with regard to seriousness, severity, and relatedness to the study treatment for recording in the CRF.

Seriousness
International Conference on Harmonization (ICH) Guidelines define a serious adverse event (SAE) as any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires or prolongs existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Important medical events that may not result in death, be life-threatening or require hospitalization, but that may jeopardize the patient or require medical intervention to prevent one of the above outcomes, should also be considered serious when based upon the Investigator's medical judgment.

Events not to be reported as SAEs are the following:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.

- Treatment, including hospitalization, which was elective or pre-planned for a pre-existing condition that is unrelated to the indication under study and did not worsen.
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the aforementioned definitions of "serious" and not resulting in hospital admission.

Severity
The Principal Investigator will provide an assessment of the severity of each adverse reaction by recording a severity rating on the appropriate AE reporting page of the subject's CRF. Severity will be assessed according to the following scale:

Mild – events are usually transient and easily tolerated, requiring no special treatment and causing no disruption of the subject's normal daily activities.

Moderate – events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually improved by simple therapeutic measures. Moderate experiences may cause some interference with functioning.

Severe – events interrupt the subject's normal daily activities and generally require systemic drug therapy or other treatment. They are usually incapacitating.

Relationship to Study Medication
The Investigator will assess the relationship between the study medication and the adverse event and document as follows:

Unrelated: The event is clearly due to causes other than the active study drug.

Unlikely: The event is doubtfully related to active study drug. The event was most likely related to other factors such as the patient's clinical state, concomitant drugs or other therapeutic interventions.

Possible: The event follows a reasonable temporal sequence from the time of active study drug administration, but could have been produced by other factors such as the patient's clinical state, therapeutic interventions or concomitant drugs.

Probable: The event follows a reasonable temporal sequence from the time of active study drug administration, and follows a known response pattern to the drug. The toxicity cannot be reasonably explained by other factors such as the patient's clinical state, therapeutic interventions or concomitant drugs.

Definite: The event follows a reasonable temporal sequence from the time of active study drug administration, follows a known response pattern to the drug, cannot be reasonably explained by other factors such as the patient's condition, concomitant drugs or therapeutic interventions, AND either occurs immediately following active study drug administration, improves on stopping the study drug, or reappears on re-exposure.

Adverse Events of Hypoglycemia
The CTCAE (version 4.0) criteria for mild, moderate, and severe hypoglycemia based on blood glucose will be used, as shown below:
Mild: < 70 – 55 mg/dL (< 3.8 - 3.0 mmol/L)
Moderate: < 55 – 40 mg/dL (< 3.0 - 2.2 mmol/L)
Severe: < 40 – 30 mg/dL (< 2.2 - 1.7 mmol/L)
Life Threatening: < 30 mg/dL (< 1.7 mmol/L)

Recording Adverse Events
All adverse events experienced during the trial, regardless of relationship to study medication, must be recorded on the Adverse Event CRF from the time of patient consent until completion of patients End of Study visit (Visit 9). All serious adverse events will be collected through Visit 9. The Investigator must continue to follow all non-serious events possibly related to the study medication and all serious adverse events until they resolve or until the Investigator assesses them in writing as chronic or stable.
Regardless of relationship to study medication, the event must be recorded on the Adverse Event CRF. Adverse event documentation should include the following information:

- Standard medical terminology for the AE
- Description of adverse event
- Date and time of onset
- Date and time of resolution of the adverse event
- Whether or not the event is ongoing
- Severity of the event
- Relationship between the adverse event and the investigational product
- Description of any actions taken (e.g., medications, treatments)
- Outcome of the AE
- Whether or not the effect was serious and/or unanticipated

Whenever possible, a diagnosis should be given when signs and symptoms are due to common etiology (e.g., cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). For the purposes of this study, hypoglycemic events will be considered adverse events and should be recorded in source and CRF records.
When a diagnosis is not available, each adverse event should be reported separately. For example, “nausea and vomiting” should be split into two separate events.

Reporting Serious Adverse Events
In accordance with Federal regulations, Investigators will be notified of the occurrence of serious, unexpected and related adverse events.
The Investigator must report all serious adverse events to Sponsor within 24 hours of the site being notified of the event. Investigators must also report these events to the Institutional Review Board (IRB) in accordance with the IRB’s reporting guidelines, within the IRB specified timeframe, or no later than 48 hours after knowledge of the event.

For submission of these events to the Israeli Regulatory Agency? the Sponsor will follow FDA regulations 21 CFR 312.32. If the event is determined to meet the requirements of IND Safety Reporting then expedited reporting requirements to the FDA will be followed. The Sponsor may need to issue an Investigator notification, to inform all Investigators involved in any study with the same drug (or therapy) that this serious unexpected suspected adverse reaction (SUSAR) has occurred.
Investigator Reporting Procedures
The PI or other study personnel must immediately (within 24 hours) inform Sponsor of any AE considered serious (as defined above) or otherwise medically significant. Notification should be via facsimile transmission of a written report signed by the PI. Notification must include the PI's assessment as to whether the event was or was not related to the use of the study medication. The Sponsor contact information is as follows:

Oramed Ltd.
Hi-Tech Park 2/4 Givat Ram
PO Box 39098
Jerusalem, 91390, Israel

The Principal Investigator must also promptly inform the governing IRB of the serious adverse event per the governing IRB's requirements.

The CRO will notify Oramed within 24 hours of receipt. Any SAE that occurred within 30 days after last dose will be followed and reported as above.

Pregnancy Reporting
If the subject or partner of a subject participating in the study becomes pregnant during the study or within 30 days or discontinuing study medication, the Investigator should report the pregnancy to Oramed within 24 hours of being notified. The Exposure In Utero form to the Investigator for completion.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE.

Reporting Unanticipated Problems to the IRB
The Investigator must promptly report to his or her IRB all unanticipated problems involving risks to patients. Investigators must consult FDA regulations and IRB/ethics committee guidance for reporting requirements.
Potential Adverse Events Associated with ORMD-0801
Hypoglycemia and associated symptoms (e.g., weakness, dizziness, shakiness, increased sweating, palpitations, or confusion), have been associated with insulin administration, including ORMD-0801. Animal reproductive studies have not been conducted with

ORMD-0801. It is not known whether ORMD-0801 can cause fetal harm when administered to a pregnant woman. It is also not known whether this product is excreted in human milk. Pregnant or breastfeeding women are excluded from this study.

Long-term animal studies have not been completed to assess whether ORMD-0801 impairs fertility.