Clinical Study Protocol: ORA-D-N01B

Study Title:	An Open-Label Multi-Center Study to Assess the Safety and Potential of Oral Insulin to Reduce Liver Fat Content in Type 2 Diabetes Patients with Nonalcoholic Steatohepatitis (NASH)
Protocol Number:	ORA-D-N01B
EudraCT:	2020-001046-19
Study Phase:	Phase 2
Principal Investigator:	
Sponsor:	Oramed Ltd. Mamila 20 Jerusalem, 9414908, Israel
Name of Sponsor Signatory:	Miriam Kidron, PhD Chief Scientific Officer and Director Oramed Ltd.
Protocol Version:	1.3
Date of Version:	Version 1.2: June 24, 2020
	Version 1.1: May 3, 2020
	Version 1.3: March 30, 2021
	Original (Version 1.0): April 06, 2020

SPONSOR PROTOCOL APPROVAL SIGNATURE PAGE

The undersigned has reviewed and approved Protocol No. ORA-D-N01B for issuance:

Miriam Kidron, PhD
Chief Scientific Officer and Director
Oramed Ltd.

Miriam Kidron Digitally signed by Miriam Kidron Date: 2021.04.12 14:51:26 +03'00'

Signature Date

Summary of Changes
Protocol Number ORA-D-N01B
Protocol Version 1.3 (March 30, 2021)

The following table summarizes important changes to the protocol for study number ORA-D-N01B. These changes reflect modifications made to the protocol since protocol version 1.2 (dated May 3, 2020). **Bold** font is used as needed to highlight additions and strikethrough text is uses as needed to indicate deletions from protocol version 1.2. Section Numbers refer to locations of the revised information in Protocol Amendment 02 (Version 1.3).

ITEM #	PROTOCOL ELEMENT (SECTION #)	DESCRIPTION OF CHANGE
1.	Header and Title Page	• Changed protocol version from 1.2 to 1.3. • Changed protocol date from May 3, 2020 to March 30, 2021.
2.	Synopsis and Sections 4.1 and 4.2	The following change is made to Inclusion Criterion #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 > 6.5-**11**%[28] or on treatment with **at least one** ~~on treatment with metformin only or metformin in addition to~~ **and** no more than ~~two~~ **three** of the following **oral anti-diabetic** medications**, metformin,** sulfonylurea, DPP-4 inhibitors, **oral** GLP-1 receptor agonists **(semaglutide)**, **SGLT-2 inhibitor, or** Thiazolidinediones (TZDs). The following change is made to Inclusion Criterion #9: • Females must have a negative urine pregnancy test result at screening, prior to the start of the run-in period, at initiation of active dosing and every 4 weeks till the end of the study. 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~~

ITEM #	PROTOCOL ELEMENT (SECTION #)	DESCRIPTION OF CHANGE
		~~barrier method)~~, one of which must be ~~an acceptable~~ **a** highly effective ~~barrier~~ method from the time of screening to the last study visit (22 weeks). **Highly effective methods include:** o **combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation** o **progestogen-only hormonal contraception (oral, injectable or implantable) associated with inhibition of ovulation** o **intrauterine device (IUD)** o **intrauterine hormone-releasing system (IUS)** o **bilateral tubal occlusion** o **vasectomised partner (is the sole sexual partner of the WOCBP participating in the trial)** o **sexual abstinence** **Acceptable methods include:** **Double** barrier methods of contraception include male condoms plus spermicide, diaphragm with spermicide plus male condom, cervical 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 (FSH>40), b) who are surgically menopausal (surgical sterility defined by tubal occlusion, bilateral oophorectomy, bilateral salpingectomy or hysterectomy). The following change is made to Inclusion Criterion #12: • ~~Glycaemia must be controlled (Glycosylated Hemoglobin A1C ≤8.5%) while any HbA1C increment should not exceed 1% during 6 months prior to enrolment).~~ The following change is made to Inclusion Criterion #13: • ~~Patients who are willing to participate in the study, have to have their own self-monitoring blood glucose devices.~~ The following changes are made to Exclusion Criteria #14: • Treatment with anti-diabetic medications other than **at least one and no** ~~- metformin and~~ more than ~~two~~ **three** of the

ITEM #	PROTOCOL ELEMENT (SECTION #)	DESCRIPTION OF CHANGE
		following ~~medications~~: **metformin,** sulfonylurea, DPP-4 inhibitors, **oral** GLP-1 receptor agonists **(semaglutide)**, **SGLT-2 inhibitors, or** TZDs. The following changes are made to Exclusion Criteria #15: • ~~Metformin,~~ **F**ibrates **and** statins not provided on a stable dose in the last 6 months.
3.	Section 3.2.1	The following updates were made to Screen Failure: **Subjects previously screen failed on eligibility criteria that have been updated in a protocol amendment, may be re-screened under the amendment after re-consenting.**
4.	Section 3.7	The following updates were made to Self-Monitoring Fasting Blood Glucose and Patient Diaries: • **Adverse events including hypoglycemia will be monitored from the self-monitoring blood glucose diary and recorded in the CRF.**

INVESTIGATOR SIGNATURE PAGE

I have read this protocol and agree:

- To conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs), the Declaration of Helsinki and complying with the obligations and requirements of Clinical Investigators and all other requirements listed in 21 CFR part 312 and according to the study procedures provided by Oramed Ltd. and local regulations.
- Not to implement any changes to the protocol without prior agreement from the Sponsor and prior review and written approval from the IRB or IEC, except as would be necessary to eliminate an immediate hazard to study subject (s), or for administrative aspects of the study.
- To ensure that all persons assisting me with the study are adequately informed about the Investigational Product(s) and of their study-related duties as described in the protocol.
- To completely inform all subjects in this study concerning the pertinent details and purpose of the study prior to their agreement to participate in the study in accordance with GCP and regulatory authority requirements.
- To be responsible for maintaining each subject's consent form in a secure study file and providing each subject with a signed copy of the consent form.
- That I am thoroughly familiar with the appropriate use of the Investigational Product(s), as described in the protocol, and any additional information provided to me by, or on behalf of Oramed Ltd.

Principal Investigator (Name and Title)	Signature	Date

STATEMENT OF COMPLIANCE

The study will be carried out in accordance with Good Clinical Practice (GCP) as required by the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46; 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312)
- E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) (2018)

All key personnel (all individuals responsible for the design and conduct of this study) have completed Good Clinical Practice Training.

Contents

SYNOPSIS

Title	An Open-Label Multi-Center Study to Assess the Safety and Potential of Oral Insulin to Reduce Liver Fat Content in Patients with Nonalcoholic Steatohepatitis (NASH)
Indication	Nonalcoholic Steatohepatitis (NASH) and Type 2 Diabetes Mellitus (T2DM)
Clinical Phase	Phase 2
Test Product Details	ORMD-0801 (insulin) capsule **Dose:** Two capsules of 8 mg each **Dosage Form:** Soft gel capsule (1 capsule contains 8 mg of insulin) **Mode of Administration:** Oral
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.
Total Sample Size	Up to 40 patients with NASH and Type 2 DM will be enrolled in this multi-center study.
Study Design	This is an open, multi-center 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 Endpoints	The primary endpoint of this trial will evaluate safety of ORMD-0801 in patients with nonalcoholic steatohepatitis (NASH) and type 2 DM. Secondary endpoints will evaluate the effectiveness of ORMD-0801 in reducing liver fat content in patients with NASH and type 2 DM by measuring the final and baseline differences in the MRI as liver function tests.
Summary of Assessments	**Safety Assessments:** Safety will be assessed by monitoring adverse events including hypoglycemia, physical exam, vital signs (blood pressure heart rate and oral temperature), ECG and clinical laboratory assessments. **Efficacy Assessments:**

	Efficacy will be assessed by measuring the final and baseline differences in fat content obtained from MRI and Fibroscan results.
Duration of Participation	Screening Phase**:** up to 42 days prior to enrolment Placebo run-in Phase: 2 weeks Treatment Phase: 12 weeks End-of-Study (EOS): After completion of 4 weeks after end of treatment
Subject Selection Criteria	**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 > 6.5-11%[28] or on treatment with at least one and no more than-three of the following oral anti diabetic medications metformin, sulfonylurea, DPP-4 inhibitors, oral GLP-1 receptor agonists (semaglutide), SGLT-2 inhibitor, orThiazolidinediones (TZDs) 4. Diagnosis of NAFLD by non-invasive determination of hepatic steatosis grade S1, defined as hepatic steatosis>8%. by MRI- PDFF and CAP FibroScan ≥ 238 dB/m. 5. Liver enzyme abnormalities: ULN≤5 times. 6. Fibrosis score 1≤F≤3 as defined by FibroScan measurement (Liver stiffness measurement, LSM) of 6 ≤ LSM≤12 kPa. 7. Signature of the written informed consent. 8. Negative pregnancy test at study entry for females of childbearing potential. 9. Females must have a negative urine pregnancy test result at screening, prior to the start of the run-in period, at initiation of active dosing and every 4 weeks till the end of the study. 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, one of which must be a highly effective method from the time of screening to the last study visit (22 weeks). Highly effective methods include: o combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation o progestogen-only hormonal contraception (oral, injectable or implantable) associated with inhibition of ovulation o intrauterine device (IUD) o intrauterine hormone-releasing system (IUS) o bilateral tubal occlusion o vasectomised partner (is the sole sexual partner of the WOCBP participating in the trial) o sexual abstinence

	Acceptable methods include: Double barrier methods of contraception include male condoms plus spermicide, diaphragm with spermicide plus male condom, cervical cap with spermicide plus male condom. 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 (FSH>40), b) who are surgically menopausal (surgical sterility defined by tubal occlusion, bilateral oophorectomy, bilateral salpingectomy or hysterectomy). 10. 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 11. 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 enrolment and up to the end of the study. **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 enrolment. 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 (264.6 lbs.). 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 enrolment. 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 (2 units/day) for women and >30 g/day (3 units/day) for men. 14. Treatment with anti-diabetic medications other than at least one and no more than-three of the following medications: metformin, sulfonylurea, DPP-4 inhibitors, oral GLP-1 receptor agonists (semaglutide), SGLT-2 inhibitors, or TZDs 15. Fibrates and 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 (ULN). 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 (ULN). Patients with a reason for CPK elevation may have the measurement repeated prior to enrolment; a CPK retest > 3X ULN leads to exclusion. 22. Subjects meeting criteria for contraindication for MRI – including the following: • History of severe claustrophobia impacting ability to perform MRI during the study, even despite mild sedation/treatment with as anxiolytic. • Subjects with metal implants, devices, paramagnetic objects contained within the body and excessive or metal containing tattoos. • Subjects unable to lie still within the environment of the MRI scanner or maintain a breath hold for the required period to acquire images, even despite mild sedation/treatment with an anxiolytic. 23. Subject participated in a clinical research study involving a new chemical entity within 4 weeks of study entry. 24. Known allergy to soy.
Statistical Methods	Descriptive statistics (mean, standard deviation, median, minimum, and maximum values) will be tabulated for the study population. Subject disposition, demographic and Baseline characteristics, extent of exposure and study termination/withdrawal information will be presented. Descriptive statistics will be presented for each of the evaluable safety and efficacy parameters for change from Baseline as well as value at each time point. Adverse event information will be summarized by age group and

	narratives were used in presentation of the data for safety monitoring. Serious adverse events (SAEs) will be summarized similarly and narratives presented. Clinical laboratory values will be summarized by time point, subject, and age group. Values and changes from baseline at each time point will be tabulated.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
BUN	blood urea nitrogen
CAP-Fibroscan	controlled attenuation parameter-Fibroscan
CBC	complete blood count
CFR	code of federal regulations
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
ECG	electrocardiogram
EDTA	ethylenediaminetetraacetic acid
EOS	End-of-Study
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HbA1C	hemoglobin A1C
HOMA	The Homeostasis Model Assessment
IBD	inflammatory bowel disease
ICH	International Conference on Harmonization
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
LFT	Liver Function Test
MedDRA	Medical Dictionary for Regulatory Activities
MRI-PDFF	MRI-Proton Density Fat Fraction
NAFDL	Nonalcoholic fatty liver disease
NAFL	Nonalcoholic fatty liver
NASH	Nonalcoholic Steatohepatitis
PE	physical exam
PHI	protected health information
SAEs	serious adverse events
SBP	systolic blood pressure
SBTI	soybean trypsin
SOPs	standard operating procedures
SUSAR	suspected adverse reaction
T2DM	Type 2 Diabetes Mellitus
TEAE	treatment-emergent adverse event
TSH	Thyroid Stimulating Hormone
ULN	upper limit of normal

WHO	World Health Organization

1 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.

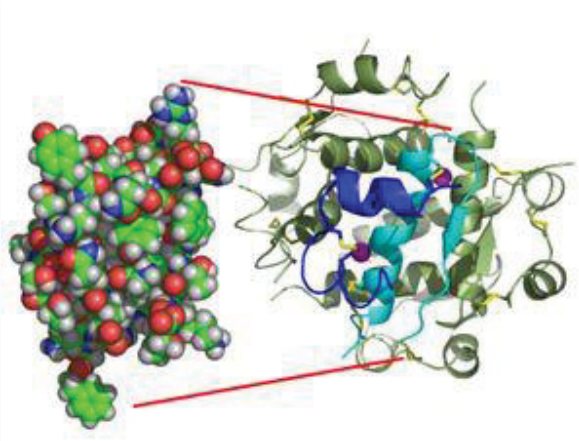
To overcome these barriers, Oramed has proposed a mechanism to prevent the digestion of the introduced hormone in the gastrointestinal tract and to facilitate its physiological absorption. After performance of a range of studies for optimization of co-factors to prevent the digestion of insulin, Oramed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

2 STUDY OBJECTIVES

2.1 Primary Objectives

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

2.2 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.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an open, multi-center study using the oral ORMD-0801 insulin formulation in patients with NASH and confirmed type 2 DM. This exploratory multi-center study will enroll 40 patients with NASH and type 2 DM between the ages of 18 and 70. Subjects will undergo a screening phase up to 42 days prior to enrolment for 2 weeks, a treatment phase for 12 weeks and an end-of-study phase after completion of 4 weeks, after end of treatment.

At screening (Visit 1, up to week -6), subjects will sign the ICF and inclusion and exclusion criteria will be reviewed. Medical history, demographics (sex, age, race and ethnicity), and prior and concomitant medications will be recorded. Height and weight will be measured, and BMI will be calculated. Vital signs (SBP/DBP, heart rate and oral temperature), complete physical examination, 12-Lead ECG, clinical laboratory evaluations, urine pregnancy test for females of childbearing potential, blood lipids test, HbA1c, viral serology, CAP-Fibroscan and MRI-PDFF will be performed. For females of non-childbearing potential, FSH levels will be tested if results are not available. Adverse events will be monitored and recorded.

After Screening, each subject will undergo a placebo run-in phase (Visit 2, to Week -2). Concomitant medications will be reviewed. All subjects will receive the morning treatment (run in placebo) in clinic, 1 bottle of placebo medication and subject diaries will be dispensed. Vital signs (SBP/DBP, heart rate and oral temperature) and weight will be collected. Fasting blood glucose and fasting insulin will be measured, urine pregnancy test will be performed for females of childbearing potential. Self-monitored fasting morning blood glucose (finger-stick) will be recorded in the patient diaries 3 days weekly in the morning. Adverse events will be monitored and recorded.

Subjects will then undergo a treatment phase consisting of a treatment period of 12 weeks that will start at Visit 3 (Week 0) and outpatient visits at Weeks 1, 2, 4, 8, and 12 (final visit). At each visit, concomitant medication will be reviewed, weight will be measured, ORMD-0801 morning treatment will be administered in clinic, and sufficient quantity of medication will be dispensed to last until the next nominal clinic visit. Medication compliance check will be performed, self-monitored fasting morning blood glucose (finger-stick) will be recorded 3 days weekly in the morning and subjects' diaries will be reviewed. Vital signs (SBP/DBP, heart rate and oral temperature) will be recorded. Adverse events will be monitored and recorded.

At Visit 3, urine and serum pregnancy test will be performed for females of childbearing potential. Additional urine serum pregnancy test will be performed for females of childbearing potential at visits 6, 7 and 8. At Visit 8, subjects will have HbA1c evaluations and MRI-PDFF performed. At Visits 3 and 8, a complete physical exam and fibroscan will be performed.

The end of the study (EOS) Visit (Visit 9) will be conducted 4 weeks following the last scheduled treatment visit. Subjects concomitant medications will be reviewed, and weight will be measured. A complete physical exam and ECG will be performed and vital signs (SBP/DBP, heart rate and oral temperature) will be measured if deemed necessary by the investigator. Clinical laboratory evaluation will be performed. Fasting blood glucose, fasting insulin, HbA1c,

blood lipids and adiponectin levels will be measured. Urine serum pregnancy test will be performed for females of childbearing potential. Subject diaries will be collected and reviewed for self-monitored fasting morning blood glucose. Adverse events will be monitored and recorded. Subjects who are discontinued early from the study will complete the EOS evaluations at the time of early discontinuation.

3.2 Screening/Visit 1 (up to week -6)

Screening process will take place at Visit 1, up to 42 days prior to enrolment. Screening activities will consist of the following:

Visit 1 (up to week -6)

- Informed consent
- Medical history
- Concomitant medication
- Complete Physical examination (PE)
- Weight and height
- ECG
- Vital signs (blood pressure, heart rate, oral temperature). Vital signs will be measured in the sitting position after at least 5 minutes of rest.
- Urine pregnancy test
- Females of non-childbearing potential FSH levels will be tested if results not available.
- Clinical laboratory evaluations
    - Chemistry: Electrolytes, Blood Urea Nitrogen (BUN), international normalized ratio (INR), creatinine, glucose level, liver function tests (LFT) including transaminases (ALT, AST), albumin, and alkaline phosphatases, creatine phosphokinase (CPK), Bilirubin
    - Hematology: Complete blood count (CBC)
    - Thyroid Stimulating Hormone (TSH)
    - HbA1C
    - Blood lipids: Total cholesterol, LDL, HDL, Triglycerides
    - Viral serology: HCV-Ab, HBsAg, HBcore-total, HBs Ab, anti-HIV Ab
- CAP - Fibroscan
- MRI-PDFF
- AE/SAE assessment

For subjects who meet eligibility criteria based on the Screening assessments, instruction will be provided on the following:

- the use of adequate contraceptive methods (see Section 4.1) for the duration of the study (Screening through End of Study (Visit 9);
- minimal use of concomitant medications during the study, if possible, and avoid prohibited medications as defined in Section 5.6;
- maintenance of usual dietary habits and avoidance of drastic changes, such as a conversion to a vegetarian diet;

- restraint from excessive alcohol use or binge drinking during the study, and restraint from drinking alcohol from 72 hours prior to all study visits;
- restraint from excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) during the study.

3.2.1 Screen Failure

A screen failure is defined as a subject who has signed the ICF, does not meet all the entry criteria outlined in Section 4 of this protocol. Note that this includes assessments through Visit 1 (up to Days -42), prior to receiving IMP.

The Investigator is responsible for keeping a record of all subjects screened for entry into the study and subsequently excluded. The reason(s) for exclusion will be recorded in the source documents and on the Screening log.

Subjects previously screen failed on eligibility criteria, may be re-screened after re-consenting at the discretion of the treating physician.

3.3 Run-in Phase/Visit 2 (to week -2)

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

3.3.1 Visit 2 (to week -2)

- Concomitant medication
- Weight
- Morning placebo administration (run-in placebo)
- Vital Signs
- Urine pregnancy test
- Fasting blood glucose and fasting Insulin
- Self-monitored fasting morning blood glucose (finger-stick) recorded in the patient diaries 3 days per week in the morning.
- Dispense 1 bottle of Placebo - Patients will take 2 capsules daily of Placebo in the morning, 30 to 45 minutes prior to breakfast and no later than 10 AM for 2 weeks.
- AEs/SAEs assessmentAEs/SAEs assessment

3.4 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 3 (baseline) and visits at week 1, 2, 4, 8, and 12 (final visit).

At each visit patients will have:

- Concomitant medication
- Weight
- Morning treatment administration of oral ORMD-0801 insulin formulation
- Medication Compliance check.
- Urine pregnancy test at visit 3 prior to active dosing and at visits 6, 7, 8 and 9.
- Serum pregnancy test at visit 3 prior to active dosing

- Vital signs (blood pressure, heart rate, oral temperature). Vital signs will be measured in the sitting position after at least 5 minutes of rest.
- Self-monitored fasting morning blood glucose (finger-stick) of fasting blood
- AEs/SAEs assessment

3.4.1 Visits 3 (baseline), 6, 7, and 8

- 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)[1]
- Adiponectin
- Blood lipids: Total cholesterol, LDL, HDL, Triglycerides

3.4.2 Visits 3 (baseline), 5, 6, 7, and 8

- Return capsules - check compliance
- At visit 3 and 5 - Dispense 1 bottle of ORMD-0801
- At visits 6 and 7 – dispense 2 bottles of ORMD-0801
- Patients will take 2 capsules daily of ORMD-0801 in the morning, 30 to 45 minutes prior to breakfast and no later than 10 AM for 12 weeks.

3.4.3 Visits 3 and 8

At Visits 3 and 8 patients will have:

- Complete PE
- Fibroscan

3.4.4 Visit 8

At visit 8 Patients will have:

- HbA1C
- MRI-PDFF

3.5 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:

- Concomitant medication
- Complete PE, only if the investigator deems it necessary.
- Weight
- ECG, only if the investigator deems it necessary.
- Vital signs (blood pressure, heart rate, oral temperature) will be measured in the sitting position after at least 5 minutes of rest, only if the investigator deems it necessary.

[1] HOMA = The Homeostasis Model Assessment

- Clinical laboratory evaluations (chemistry, hematology)
- Fasting blood glucose and fasting Insulin
- Blood lipids: Total cholesterol, LDL, HDL, Triglycerides
- Adiponectin
- HbA1C
- Urine pregnancy test
- AEs/SAEs assessment

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

3.6 Unscheduled visit

The patient may be required to return to the clinic in the morning following a 10-hour fast for an unscheduled Visit for a repeat measurement of fasting blood glucose and any necessary clinical safety laboratory assessments if the investigator deems it necessary. AEs/SAEs assessment will also be performed.

3.7 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. Adverse events including hypoglycemia will be monitored from the self-monitoring blood glucose diary and recorded in the CRF.

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. 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 patient is invited for an unscheduled visit, blood will be drawn and sent to lab for plasma glucose determination. 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.

If a fasting blood glucose value is <70 mg/dL, the patient should drink 1 cup of orange juice or swallow 3-4 glucose tablets. The patient must check his blood sugar after 10 min and if the blood glucose level does not raise, the patients needs to drink another cup of orange juice or swallow 3-4 glucose tablets. Blood sugar must be checked again after 10 minutes. The patient must call to report this event to the study site and record all blood glucose levels in the diary.

If three or more fingerstick glucose values of <50 mg/dL (2.78 mmol/L) 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.

3.8 Schedule of Events

Table 1 below describes the daily schedule of events from Screening Visit 1 through End of the Study Visit 9.

Table 1: Daily Schedule of Events from Screening Through Visit 9

Assessments	Screening	Placebo	Treatment						Un Scheduled Visit	End-of-Study / Early Termination
Week	**up to -6**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**Not Defined**	**16**
Days	**Up to -42**	**-14**	**0± 4**	**7± 4**	**14± 4**	**28± 4**	**56± 4**	**84± 4**		**112±4**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Un Scheduled**	**9**
Written informed consent	X									
Collection of Demographics	X									
Inclusion/ Exclusion	X									
Medical history	X									
Concomitant medication	X	X	X	X	X	X	X	X		X
Complete physical examination	X		X					X		(X[1])
Height and weight and BMI	X									
Weight		X	X	X	X	X	X	X		X
Urine pregnancy	X	X	X			X	X	X		X
Serum pregnancy			X							
FSH[3]	X									
Morning treatment in clinic		X	X	X	X	X	X	X		

Medication dispensing		X	X		X	X	X			
Medication compliance check			X	X	X	X	X	X		
ECG	X									(X[1])
Vital signs[4]	X	X	X	X	X	X	X	X		(X[1])
Clinical laboratory evaluations[5]	X		X			X	X	X	(X[1])	X
Fasting blood glucose and fasting Insulin[6]		X	X			X	X	X	(X[1])	X
Self-monitored fasting morning blood glucose[7]		X	X	X	X	X	X	X		
Adiponectin			X			X	X	X		X
HbA1C	X							X		X
Blood lipids: Total cholesterol, LDL, HDL, Triglycerides	X		X			X	X	X		X
Fibroscan Test	X		X					X		
MRI PDFF	X							X		
Viral serology[8]	X									
TSH	X									
AE/SAE assessment[9]	X	X---------->								

[1]Only if investigator deems necessary
[2]Blood samples taken prior to dosing in clinic and snack provided after 30-45 minutes at V2, 3, 6, 7, and 8[3]Vital signs (blood pressure, heart rate, oral temperature). Vital signs will be measured in the sitting position after at least 5 minutes of rest.
[3]For females of non-childbearing potential, FSH levels will be tested if results are not available
[4]Vital signs (blood pressure, heart rate, oral temperature). Vital signs will be measured in the sitting position after at least 5 minutes of rest.
[5]Chemistry and hematology: electrolytes, Blood Urea Nitrogen (BUN), international normalized ratio (INR), creatinine, glucose, bilirubin, Liver Function Tests (LFTs) and Complete Blood Count (CBC)
[6]Fasting blood glucose and insulin will be used to determine Homeostasis Model Assessment (HOMA) estimates.

[7]Self-monitoring (finger-stick) of fasting blood glucose will required 3 days weekly in the morning, before breakfast, and recorded in patient diaries.
[8]HCV-Ab (hepatitis C virus antibody), HBsAg (surface antigen of the hepatitis B virus), HBcore-total (total hepatitis B core antibody), HBs Ab (hepatitis B surface antibody), anti-HIV Ab (human immunodeficiency virus antibody).
[9]Adverse events will be collected throughout the study beginning from the time the patient signs the consent form until the EOS evaluations

4 STUDY SUBJECT SELECTION

4.1 Inclusion Criteria

Each subject must meet all of the following criteria to be eligible for the study:

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 > 6.5-11%[28] or on treatment with at least one and no more than-three of the following oral anti-diabetic medications metformin, sulfonylurea, DPP-4 inhibitors, oral GLP-1 receptor agonists (semaglutide), SGLT-2 inhibitor or Thiazolidinediones (TZDs).
4. Diagnosis of NAFLD by non-invasive determination of hepatic steatosis grade S1, defined as hepatic steatosis>8%. by MRI- PDFF and CAP FibroScan ≥ 238 dB/m.
5. Liver enzyme abnormalities: ULN≤5 times.
6. Fibrosis score 1≤F≤3 as defined by FibroScan measurement (Liver stiffness measurement, LSM) of 6 ≤ LSM≤12 kPa.
7. Signature of the written informed consent.
8. Negative pregnancy test at study entry for females of childbearing potential.
9. Females must have a negative urine pregnancy test result at screening, prior to the start of the run-in period, at initiation of active dosing and every 4 weeks following till the end of the study. 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 , one of which must be a highly effective method from the time of screening to the last dosing study visit (22 weeks).

   Highly effective methods include:
   - combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal or transdermal) associated with inhibition of ovulation
   - progestogen-only hormonal contraception (oral, injectable or implantable) associated with inhibition of ovulation
   - intrauterine device (IUD)
   - intrauterine hormone-releasing system (IUS)
   - bilateral tubal occlusion

   Acceptable methods include:
   Double barrier methods of contraception include male condoms plus spermicide, diaphragm with spermicide plus male condom, cervical cap with spermicide plus male condom. 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 (FSH>40), b) who are surgically menopausal (surgical sterility defined by tubal occlusion, bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

10. 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
11. 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 enrolment and up to the end of the study.

4.2 Exclusion Criteria

Subjects who meet any of the following criteria must be excluded from the study:

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 enrolment.
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 enrolment.
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 (2 units/day) for women and >30 g/day (3 units/day) for men.
14. Treatment with anti-diabetic medications other than at least one and no more than-three of the following medications: metformin, sulfonylurea, DPP-4 inhibitors, oral GLP-1 receptor agonists (semaglutide), SGLT-2 inhibitors, or TZDs
15. Fibrates and 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 (ULN). 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 (ULN). Patients with a reason for CPK elevation may have the measurement repeated prior to enrolment; a CPK retest > 3X ULN leads to exclusion.

22. Subjects meeting criteria for contraindication for MRI – including the following:
    - History of severe claustrophobia impacting ability to perform MRI during the study, even despite mild sedation/treatment with as anxiolytic.
    - Subjects with metal implants, devices, paramagnetic objects contained within the body and excessive or metal containing tattoos.
    - Subjects unable to lie still within the environment of the MRI scanner or maintain a breath hold for the required period to acquire images, even despite mild sedation/treatment with an anxiolytic.
23. Subject participated in a clinical research study involving a new chemical entity within 4 weeks of study entry.
24. Known allergy to soy

4.3 Subject and Trial Discontinuation

Subjects may choose to withdraw from this study at any time for any reason without penalty of jeopardizing their health care or loss of benefits to which the subject is otherwise entitled.

Within the provisions of informed consent and good clinical judgment with respect to safety, every attempt will be made to have subjects complete the study. The following are reasons to terminate a subject's participation in the study:

1. Subject experiences an AE that in the judgement of the Investigator poses a significant risk to the subject for continued participation in the study.
2. Subject uses any medication that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study or that will interfere with the interpretation of the results of the study.
3. Subject becomes pregnant.
4. Significant protocol violation or noncompliance on the part of the subject or the Investigator.
5. Intercurrent illness that requires treatment that is not consistent with the protocol requirements, or intercurrent illness or the associated treatment that in the judgment of the Investigator poses a significant risk to the subject for continued participation in the study.
6. Subject wishes to withdraw for any reason.
7. Sponsor elects to end the study, or the Investigational Site elects to end the study at their site.
8. Any other reason that in the judgment of the Investigator poses unacceptable risk to the subject.

Subjects who withdraw from the study prior to treatment may be replaced. Subjects who are withdrawn and have received at least one treatment will not be replaced. Subjects who discontinue study drug treatment will not be replaced.

Except in cases of emergency, the Investigator should consult with the Sponsor and the Medical Monitor before removing the subject from the study. In some circumstances it may be necessary to temporarily interrupt treatment as a result of AEs that may have an unclear relationship to the IMP. The Investigator should obtain approval from the Sponsor and Medical Monitor before restarting IMPs that were temporarily discontinued for an AE.

In the event that a subject discontinues the study prior to completion, the date the subject is withdrawn and the reason for discontinuation will be recorded in the source documents and CRF. Although a subject will not be obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights.

All subjects who are randomized and treated (i.e., received any amount of IMP) will be included in the safety analyses. Thus, every effort will be made to contact any subject who fails to attend any follow-up appointments/contacts, in order to ensure that he/she is in satisfactory health. If a subject withdraws from the study as a result of meeting discontinuation criteria after the start of IMP administration, reasonable efforts should be made to have the subject return for the early withdrawal evaluations (Section 3.5). Any subject withdrawn due to a suspected IMP -related AE should be followed until resolution or stabilization of the event.

If a subject becomes pregnant, IMP will be discontinued immediately, and the subject will be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. The subject will be followed until delivery or other termination of pregnancy for outcome.

Subjects may choose to withdraw authorization to use and disclose their PHI. Such withdrawal of authorization must be made to the Investigator in writing. Any PHI collected by the Investigator prior to the date of such withdrawal will continue to be used and disclosed.

The Sponsor has the right to terminate this study, and the Investigator/Investigational Site has the right to close the site, at any time, although this should occur only after consultation between involved parties. The Investigator or representative will notify the IRB in writing of a premature termination of a study or closure of Investigational Site a or of a temporary halt of the study, including the reason of such an action and will send a copy of the notification to the Sponsor.

Events that may trigger premature termination of a study or closure of an Investigational Site include, but are not limited to, a new toxicity finding, a request to discontinue the trial from a regulatory authority, non-compliance with the protocol, GCP violations, slow recruitment/low enrollment, or change in development plans for the IMP.

If either of the criteria listed below is met, enrollment of new subjects and dosing of ongoing subjects will be temporarily stopped. The Investigator, Sponsor, and the Medical Monitor will discuss whether a lower dose or any additional treatment guidelines should be implemented, or if the trial should be permanently stopped. Any proposed changes to the protocol to address such findings will be submitted for review and approval by the IEC/IRB and the Competent Authority prior to re-starting the trial.

1. A death within 30 days after IMP administration where there is a reasonable possibility that the drug caused the event;
2. Two Grade 4 AEs where there is a reasonable possibility that the IMP caused the events.

5 STUDY TREATMENT (IMP)

5.1 Description of Investigational Drug

ORMD-0801

Dosage form: 2 soft gelatin capsules per dose

Strength: 8 mg insulin per capsule

Description: API (recombinant human insulin USP), in Oramed's proprietary formulation [SBTI, disodium EDTA, fish oil, aerosil, and TWEEN 80] in capsules.

5.1.1 Packaging and Labeling

This study is an open-label study. All study medication will be shipped in bulk. The Investigational Site pharmacist will be responsible for dispensing the appropriate treatment period IMP.

Study medication will be dispensed to the site with instructions for when treatment can be administered. Medication containers and any unused capsules will be retained at the study site after the treatment phase of the study is complete.

The treatment packages will be labeled with the following information:

- Study number
- Patient ID
- Bottle ID
- Dosage Form/Content
- Directions for use, including route of administration
- Number of capsules in package
- Storage conditions
- Instructions to "keep out of reach of children"
- Caution: For Clinical Trial Use Only.
- Name of Sponsor

A separate label with the identical information will be provided with the label on the package for drug accountability purposes.

5.1.2 Storage and Handling

All IMP must be kept in an appropriate, secure area to prevent unauthorized access. All IMP is to be shipped under refrigerated conditions and stored in the original packaging at controlled temperature (36 to 46°F; 2 to 8°C). Excessive humidity should be avoided. Storage conditions will be monitored, and appropriate monitoring logs maintained as source data. Deviations from the established temperature, as well as the occurrence of excessive humidity, should be documented, and the Sponsor should be notified.

IMP should be handled and disposed, using proper procedures as defined by Investigational Site standard operating procedures (SOPs) for Investigational Drugs.

Investigator will be supplied with a sufficient amount of study medication in order to provide each subject with sufficient treatment. Site will document their inspection of shipments of study medication and notify the Sponsor of any breakage, shortage, or other adverse shipment events.

5.2 IMP Administration

5.2.1 Visit 3 to Visit 8

The treatment regimen (Active) will consist of a soft gelatin capsule containing 8 mg insulin, and 75 mg SBTI. Patients will take 2 capsules daily in the morning 30 to 45 minutes prior to breakfast and no later than 10AM. At Visit 2 (placebo) and at Visits 3, 6, 7, 8 (Active) capsules will be administered in the clinic. Blood samples and weights will be taken prior to dosing, after which the patients will take the drug, so he\she will be provided with a small snack to eat after 30 to 45 minutes.

5.3 Dose Modifications

This study does not include any planned dose modifications. From Visit 3 to Visit 8, subjects will daily take the IMP orally at the assigned dose level unless discontinuation criteria as defined in Section 4.3 are met.

5.4 Measuring Subject Compliance

All treatments on visit days will be administered in the, Clinical Research Unit. Compliance for oral capsules (Visit 3 to Visit 8) will be assessed through a count of unused study medication during clinic.

5.5 Drug Accountability

In accordance with current GCP, the Investigational Site will account for all IMP supplies. Details of receipt, storage, administration, and return or destruction will be recorded in the Investigational Drug accountability record according to the SOP of the Investigational Site. Copies of the Investigational Drug accountability record will be provided to the Sponsor.

IMP will only be dispensed to subjects enrolled in this protocol, and only as directed by this protocol. Administration of IMP will be accurately recorded in each subject’s source documents and CRF. Study participants will be dispensed sufficient quantities of study treatment to last until the next nominal clinic visit. Study participants will be asked to return all unused study medication for accountability at each clinic visit. Compliance with study medication is monitored and recorded by site personnel by counting the remaining study medication.

At the conclusion of the study, study drug supplies (including partially used packages) will be returned or destroyed according to instructions provided by Oramed Ltd. Drug destruction procedures and documentation must be retained at the site.

5.6 Concomitant Medications and Supplements

All prior medications and supplements taken within 30 days prior to the first dose of IMP and concomitant medications and supplements will be recorded in the subject's source documentation and in the CRF.

Any concomitant medication use will be evaluated on a case-by-case basis by the Investigator. If a subject requires the use of any medications, the Investigator will contact the Sponsor and the Medical Monitor to discuss the subject's continued participation in the study. In the event of an emergency, subjects will be treated at the discretion of the Investigator according to acceptable community standards of medical care.

5.7 Behavioral Restrictions

Subjects should arrive following a minimum 10-hour fast and must not take any food prior to scheduled dosing as described in the study design. Water intake will be unrestricted. All subjects will continue with their regular diet.

Excessive caffeine use (i.e., more than five cups of caffeinated beverages per day) will not be allowed from Screening through Visit 8. Excessive alcohol use or binge drinking will be discouraged during the study, and alcohol will be prohibited 72 hours prior to each visit. Subjects must refrain from tobacco or nicotine use throughout the study. Subject should not use any recreational or illicit drugs throughout the study.

Subjects will also be asked to refrain from any unusual or unaccustomed vigorous exercise during the course of the study.

6 STUDY PROCEDURES AND ASSESSMENTS

6.1 Informed Consent

According to the ICH guideline for GCP (E6) and all institutional local and state laws, the Investigator will obtain and document informed consent for each subject screened for this study. All subjects will be informed in writing of the nature of the protocol and Investigational Drug, its possible hazards, and their right to withdraw at any time, and will voluntarily sign a form (ICF) indicating their consent to participate in the study prior to the initiation of study procedures. The subject's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the Investigator's designated IRB and by Oramed Ltd. designee prior to its use. Refer to Section 11.1.4 for further details regarding informed consent.

6.2 Demographics, Medical History and Prior Medications

At Screening, demographics (sex, age, race and ethnicity), a complete medical history and social history, including smoking, caffeine, alcohol, and drug use, will be collected by subject interview. Medications and supplements, recent blood donations, illnesses, and participation in other Investigational Drug trials or clinical trials will also be recorded.

6.3 Study endpoints

The primary endpoint of this trial will evaluate safety of ORMD-0801 in patients with nonalcoholic steatohepatitis (NASH) and type 2 DM.

Secondary endpoints will evaluate the effectiveness of ORMD-0801 in reducing liver fat content in patients with NASH and type 2 DM by measuring the final and baseline differences in the MRI as liver function tests.

6.4 Efficacy Assessments

Fat content in the liver will be assessed by measuring the final and baseline differences in the MRI and Fibroscan results.

6.5 Safety Assessments

6.5.1 Weight and Height

Height will be measured, and BMI will be calculated at Screening only with the subject wearing no shoes. Weight will be measured at all visits in fasting conditions when possible (on visits when subject is required to fast). Height will be measured at Screening only with the subject wearing no shoes, coats, jewelry and other accessories.

6.5.2 Vital Signs

Vital signs, including seated systolic/diastolic blood pressure (SBP/DBP), heart rate and oral temperature, will be recorded where indicated in Table 1. Vital signs will be measured after the subject has been sitting for at least 5 minutes in a quiet environment and prior to any blood draw

that occurs at the same time point. The recorded seated SBP/DBP value will be the mean of two measurements taken 2 minutes apart and always using the non-dominant arm.

6.5.3 Physical Examination

A complete physical examination will be performed at Screening and Visits 3 and 8. At the Investigator's discretion, an additional physical exam may be performed during the end of the study/early termination (Visit 9). The physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular; abdomen (liver, spleen); lymph nodes; and extremities, as well as an abbreviated neurological examination.

6.5.4 12-Lead ECG

A 12-lead ECG will be performed at Screening. At the Investigator's discretion, an additional ECG may be performed at the end of the study/early termination (Visit 9). The 12-lead ECG will be recorded after the subject has been resting at least 5 minutes in the supine position in a quiet environment. ECGs will be read for QT and QTc (Federicia's) intervals and clinically significant abnormalities.

6.5.5 Clinical Laboratory Tests

Blood for clinical safety laboratory assessments will be collected and processed using standard procedures at Screening and on Visits 3, 6, 7, 8 and 9 and on any unscheduled visit if the investigator deems it necessary. A local laboratory will perform all clinical laboratory tests. In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant.

6.5.5.1 Clinical Safety Laboratory Tests

The clinical safety laboratory tests will include the following hematology and serum chemistry tests:

- Hematology
  - Complete blood count (CBC)
- Serum Chemistry
  - Electrolytes
  - BUN
  - INR
  - Creatinine
  - Glucose level
  - Liver function tests (LFT) including transaminases (ALT, AST), albumin, and alkaline phosphatases, creatine phosphokinase (CPK), Bilirubin
  - Urine/serum pregnancy tests
  - TSH
  - FSH test if necessary

6.5.5.2 Additional Bloodwork

In addition to the blood tests listed above, viral serology (HCV-Ab, HBsAg, HBcore-total, HBs Ab, anti-HIV Ab), HbA1C, adiponectin and TSH will be measured according to Table 1.

6.5.6 Fasting Blood Glucose and Insulin Monitoring

During the study, both fasting finger stick glucose and laboratory fasting plasma glucose will be obtained at time points stated in Table 1. Fasting blood insulin will be used to determine HOMA estimates.

6.5.7 Pregnancy Test

A urine pregnancy test will be performed for women in child bearing years at Screening (Visit 1), Visit 2, Visit 3 and at Visits 6, 7, 8 and 9. A serum pregnancy test will be performed at Visit 3.

FSH testing to confirm menopause will be performed at Screening for women who have had more than 24 months since their last menstrual cycle, who are younger than 55 years old, and who are not surgically menopausal.

6.6 Review and Documentation of Medications and Supplements

All medications or supplements subjects are taking or have taken within 30 days prior to Visit 1 through Visit 9 will be recorded in the subject's medical record and the CRF.

All medications and supplements (other than IMP) taken by the subject after Visit 2 through Visit 8 assessments will be considered "concomitant" medications and supplements.

Medications and supplements taken prior to Visit 1 that are no longer being taken at Visit 1 will be considered "prior" medications and supplements.

Medications and supplements should be recorded according to the generic name when possible. The use of concomitant medications and supplements should be limited to those that are medically necessary. Any medication or supplement used should have an indication recorded, and for concomitant medications and supplements, this indication must be represented as either for the treatment of an AE, for the management of a pre-existing condition, or for prophylaxis.

Dosage increases for any concomitant medication or supplement should be noted and the reason for the dosage increase recorded as an AE (assumes worsening condition). The side effects of concomitant medications will be recorded as AEs.

Any subject whose condition becomes disqualifying during the course of the study may be treated for that condition. If the condition is suspected during Screening, the subject should not be enrolled. Treatment of the condition should be instituted according to the Investigator's/attending physician's judgment.

Medications that have no treatment intent but rather are part of supportive routine care such as local anesthetics, intravenous solutions to maintain fluid balance and keep access open, medications used for prophylaxis, and narcotics for postsurgical pain must also be recorded in the subject's medical record and CRF.

7 ADVERSE EVENTS AND SAFETY REPORTING

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.

7.1 Safety and Tolerability Assessments

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.

7.2 Definition of Adverse Event

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.

7.3 Adverse Events of Special Interest

7.3.1 Adverse Events of Hypoglycemia

The CTCAE (version 5.0) 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)

7.4 Definition of Serious Adverse Event

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.

7.5 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.

7.5.1 Routine Reporting of Adverse Events

All AEs, whether or not associated with the IMP that are observed by the Investigator, other Investigational Site personnel, or those reported by the subject will be recorded in the subject's source documentation and on the AE page of the CRF. Copies of the SAE CRF pages or an SAE listing generated based on the CRF pages will be submitted to the Sponsor at regularly scheduled intervals to allow the Sponsor to meet expedited regulatory reporting requirements under 21 CFR 312.32 and regular regulatory reporting requirements under 21 CFR 312.33.

For each AE, the following information will be entered in the CRF:

- Medical diagnosis of the event in standard medical terminology (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event);
- Date of onset of any new AE or worsening of a previously observed AE. For the days when the subject is in the clinic (Visit 2 to Visit 9), the time (based on a 24-hour clock) of onset should be recorded if available;
- Date of resolution of the event (or confirmation ongoing). For the days when the subject is in the clinic (Visit 2 to Visit 9), the time (based on a 24-hour clock) of resolution should be recorded if available;
- Whether the event is serious (per definition in Section 7.4), and if so, the reason it is considered serious;
- Severity of AE (per definition in Section 7.7);
- Assessment of the attributability of the AE to the IMP [per definition in Section 7.5];
- Whether the event is expected (per definition in Section 7.8);
- Action taken in treating the AE (including concomitant medications or therapies administered) and/or change in the IMP administration or dose (including whether the IMP was temporarily interrupted or discontinued);
- Outcome of AE (per definition in Section 7.9).

7.5.2 Reporting of 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 or delegate 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 or delegate of any AE considered serious (as defined above) or otherwise medically significant. Notification should be via email or 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.
Mamila 20

Jerusalem, 9414908, Israel

Contact person at Oramed:
Sharon Perles
Email: sharon@oramed.com
Phone: +972-50-8312511

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.

7.6 Causality Assessment of Adverse Events

For all AEs, the Principal Investigator will provide an assessment of causal relationship to the study medication. The causality assessment must be recorded in the subject's source documents and on the AE CRF. Causal relationship will be classified according to the following criteria:

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

2. *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.
3. *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.
4. *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.
5. *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.

7.6.1 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.

7.7 Adverse Event Severity Assessment

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.

7.8 Expectedness of Adverse Event

An unexpected AE is defined in 21 CFR 312.32(a) as follows:

> An AE is considered "unexpected" if it is not listed in the IB or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent

with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

7.9 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to ICH Topic E2B, ICH Guideline.

- **Recovered/Resolved:** The subject has recovered fully from the AE without any remaining effects or impairment.
- **Recovered/Resolved with Sequelae**: The subject has recovered, but with an after effect possibly due to disease or treatment.
- **Not Recovered/Not Resolved:** The condition is still present.
- **Fatal:** Fatal should only be used when death is possibly related to the AE.
- **Unknown**: The primary outcome is not known at the time of the final assessment. If an outcome for an AE is not available at the time of the initial report, follow-up will proceed until an outcome is known or followed up to the Final Study Visit. Any subject with a possible IMP-related AE at the Final Study Visit will be followed until resolution or stabilization of the event. Further, any SAE, whether or not related to IMP (active or Placebo), that occurs within 30 days following the last dose of IMP will be followed until resolution or stabilization of the event.

7.10 Clinical Findings

Any significant clinical findings at Visit 9 will be followed until the condition returns to pre-study status, stabilizes, or can be explained as not being IMP related. If the clinical finding is reported as an AE (per the criteria outlined in Section 7.2), the follow-up procedures for AEs defined above will apply.

8 STATISTICAL METHODS

This section describes the statistical methods to be used for the analysis and reporting of data collected under Protocol No. ORA-D-N01B. Additional details will be provided in the statistical analysis plan.

8.1 Sample Size

Up to 40 patients with NASH and Type 2 DM will be enrolled in this multi-center exploratory study. Approximately 20 patients will be enrolled at 2 sites in Israel, approximately 10 subjects will be enrolled at 3 or 4 sites in Belgium and 10 patients at 2 sites in the USA.

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 30 to 45 minutes prior to breakfast.

The size of the study population was determined by reviewing the literature for pilot studies and was found to be sufficient to show trends of reducing liver fat content by MRI PDFF (MRI-Proton Density Fat Fraction) images and Fibroscan including CAP. This study is not powered for statistical significance.

8.1.1 Populations

Safety Population: All subjects who receive at least one dose of IMP will be included in the safety population.

Intention to Treat: All subjects who were received treatment were included in the Intention to Treat population.

Per Protocol: All subjects who completed all study visits without any major protocol deviations and took between 80% and 120% of Investigational Product were included in the Per Protocol population.

8.2 Safety Evaluation

8.2.1 Adverse Events

AEs will be coded using the most current version of MedDRA. The severity of AEs will be graded according to NCI CTCAE version 4.03. AEs will be regarded as “pretreatment” if they occur during the Placebo run-in period. TEAEs are defined as any AE that starts or increases in severity after the first dose of IMP at Visit 3.

The incidence of TEAEs will be tabulated by MedDRA preferred term, system organ class, treatment group, severity, and assigned relationship to IMP. The incidence for each TEAE will be provided as the total number of subjects that experienced the TEAE, as well as the percentage of the population that this represents. If a TEAE is reported more than once for a given subject, the greatest severity and the worst-case attribution will be presented in the summary tables.

TEAEs will be listed for individual subjects, along with information regarding onset and end dates, onset time where available, severity, seriousness, relationship to IMP, action taken, and outcome. A similar listing will be prepared for the pretreatment AEs.

Pretreatment AEs and TEAEs that lead to withdrawal from the study will be separately listed and summarized. Similarly, separate tabulations and listings will be prepared for pretreatment and treatment-emergent SAEs.

Descriptive statistics will be generated as appropriate (i.e., frequency for categorical data). Inferential statistical analysis comparing the AE data between Active treatment and Placebo is not planned.

8.2.2 Laboratory Evaluations

Individual clinical safety lab (hematology, serum chemistry and serology) values will be listed by visit and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data). Individual change from baseline (Screening) in laboratory values will be calculated and summarized descriptively. Shift tables from baseline (Screening) to post-dose (Visit 8) will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from baseline will be recorded as an AE if deemed appropriate by the Investigator.

8.2.3 Vital Signs

Individual vital sign measurements (seated SBP/DBP, heart rate and oral temperature) will be listed by measurement time and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation). Individual change from baseline (screening) in vital sign measurements will be calculated and summarized descriptively. A clinically significant change from baseline will be recorded as a TEAE if deemed appropriate by the Investigator.

8.2.4 12-lead ECG

Individual 12-lead ECG assessments will be listed by visit and summarized using descriptive statistics as appropriate (i.e., mean, median, range, and standard deviation for continuous data and frequency for categorical data).

8.2.5 Physical Examination

Individual physical examination findings will be listed by visit. A clinically significant change from baseline (Screening) will be recorded as an AE if deemed appropriate by the Investigator.

8.2.6 Prior and Concomitant Medications and Supplements

Medications and supplements will be coded using the most current version of the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.

All medications and supplements (other than IMP) taken by the subject from Visit 3 through Visit 8 will be considered “concomitant” medications and supplements. Medications and supplements taken prior to Visit 2 that are no longer being taken at the time of Visit 2 will be considered “prior” medications and supplements.

Concomitant medications and supplements will be listed for individual subjects. A similar listing will be prepared for prior medications and supplements taken within 30 days prior to the first dose of IMP. The incidence of these prior and concomitant medications and supplements will be summarized.

8.2.7 Handling of Missing, Unused, or Spurious Data

Descriptive statistics and listings will be provided for all data. No substitution of missing data will be used in any calculations. Data points that appear to be spurious will be investigated and will not be excluded from the listings. Influential cases will be handled in an appropriate statistical manner.

9 DATA HANDLING AND RECORD KEEPING

9.1 Data Quality Assurance

Site visits will be conducted to verify the qualifications of each Investigator, inspect the study center facilities, and inform the Investigators of their responsibilities and the procedures for ensuring adequate and correct documentation.

Investigator training will be held to introduce Investigators and their study staff to the clinical protocol, CRFs, study procedures, regulatory requirements, and use of the study assessments.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the CRFs for this study must be consistent with the patient's source documentation (i.e., medical records).

9.2 Case Report Forms

CRF's are provided for each patient. The site will be trained in the use and completion of the CRFs. All forms must be filled out as instructed by appropriate personnel who have undergone CRF training. Data will be entered into the CRF as information becomes available on a visit-by-visit basis. All data recorded on the CRF's should be supported by source documentation including completed patient diaries which will act as the source for this study. Only incidences where the data is only recorded once in the CRF will the CRF act as source and additional supporting source documentation is not warranted. The study completion information page of the CRF must be signed and dated by the Principal Investigator.

All CRF corrections are to be made by an Investigator or other study site personnel. The Principal Investigator or Sub-Investigator must authorize changes to the recorded safety and efficacy data, and this authorization must be documented in the source documents.

The Investigator or Sub-Investigator will sign and date the indicated places of the CRF. This signature will indicate that thorough inspection of the data therein has been made and will thereby certify the contents of the form. Documentation of procedures and visits will also be maintained in source documents and signed by the Investigator or Sub-Investigator.

CRFs will be scanned and later mailed to the sponsor in Israel.

9.3 Source Documents

The Investigator will permit study-related monitoring, audits by or on behalf of the Sponsor, IRB/Independent Ethics Committee (IEC) review and regulatory inspections providing direct access to source data documents. Source documents are original records in which raw data are first recorded. These may be office/clinic/hospital records, charts, diaries, x-rays, laboratory results, printouts, pharmacy records, care records, and completed scales for each study participant. Source documents should be kept in a secure area with limited access. All source documents must be accurate, clear, unambiguous, permanent and capable of being audited. They should be made using a permanent form of recording (ink, typing, printing, optical disc etc). They should not be obscured by correcting fluid or have temporary attachments (such as removable self-stick notes).

Source documents that are computer generated and stored electronically must be printed, signed and dated by the Investigator.

Source data for patients registered to the study should indicate the date the informed consent form (ICF) was signed, clinical protocol number and title, treatment number, and evidence that inclusion/exclusion criteria have been met.

9.4 Direct Access to Source Data and Study Audits

Site monitors will perform onsite visits to review protocol compliance, compare CRFs and individual patient's source records, assess drug accountability, check for CRF completeness and clarity, and ensure that the study is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Representatives of the IRB, FDA, and/or the Sponsor may also wish to carry out such data checks during onsite audit inspections. Direct access to source data will be required with due consideration to data protection and medical confidentiality.

9.5 Study Monitoring

Monitoring of the study is the responsibility of the Sponsor and may be delegated to a contract research organization (CRO) or a contract monitor. The study monitor will advise the Investigator regarding the practical conduct of the study and maintaining compliance with the protocol, Good Clinical Practice (GCP) and all applicable regulatory requirements.

Before study initiation, at a site initiation visit or at an Investigator’s meeting, a study monitor will review the protocol and CRFs with the Investigator and his staff.

Throughout the course of the study, the study monitor will oversee the conduct and the progress of the study by frequent contacts with the Investigator. This will include telephone calls and on-site visits. During the on-site visits, the CRF will be reviewed for completeness with corresponding source documents. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and will periodically request review of the Investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Periodically, some or all of the facilities used in the study (e.g. local laboratory, pharmacy) may be reviewed. Monitoring visits will be arranged in advance with site personnel at a mutually acceptable time. Sufficient time must be allowed by the site personnel for the monitor to review CRFs and relevant source documents. The Investigator should be available to answer questions or resolve data clarifications. The Investigator or appointed delegate will receive the study monitor during these on-site visits; cooperate in providing the documents for inspection and respond to inquiries.

The Investigator will ensure that the study participants are aware of and consent that personal information may be scrutinized during the data verification process as part of study-related monitoring and auditing by properly authorized persons associated with Oramed or inspection by domestic and/or foreign regulatory authority(ies). However, participation and

personal information should be treated as strictly confidential to the extent that the applicable law permits, and not be publicly available.

9.6 Study Close-Out

Upon completion of the study (defined by all patients have completed all follow-up visits, all CRFs are complete, and all queries have been resolved), the study monitor will notify the sites accordingly, and a study closeout visit will be performed. The study monitor will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB of study closure.

9.7 Archiving Study Records

Study documentation must be retained for a minimum of two years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or until at least two years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents may be retained for a longer period if required by the applicable legal requirements.

10 AMENDMENTS/MODIFICATIONS TO THE PROTOCOL

The Investigator will ensure that the study is conducted in accordance with the procedures and evaluations described in this protocol. As the study progresses it may become necessary to change or modify parts of the protocol. The Sponsor or designee is responsible for submitting protocol amendments to the appropriate government regulatory authorities. The Investigator is responsible for submitting protocol amendments to the appropriate IRB. Approval by the IRB must be obtained before changes are implemented.

When an emergency occurs that requires a departure from the protocol for an individual, a departure will be only for that subject. The Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the Medical Monitor immediately by telephone. Such contacts will be made as soon as possible to permit a decision as to whether or not the subject (for whom the departure from protocol was affected) is to continue in the study. The CRF and source documents will completely describe the departure from the protocol and state the reasons for such departure. In addition, the IRB will be notified in writing of such departure from protocol.

11 INVESTIGATOR OBLIGATIONS

11.1 Regulatory Documentation

Before the trial starts, Essential Documents as defined in ICH E6, will be generated and placed in both the Investigator's and Sponsor's files. Additional Essential Documents will be added to both files as new information becomes available and at the completion or termination of the trial as defined in ICH E6.

11.2 Protection of Human Subjects

11.2.1 Declaration of Helsinki

The Investigator will conduct this study in accordance with the Declaration of Helsinki (1964) including all amendments up to and including the October 2013 revision.

11.2.2 Good Clinical Practice and Regulatory Compliance

The Investigator will conduct this study in accordance with the principles of GCP (current ICH guidelines) and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects.

The study will be conducted as described in the approved protocol, with amendments and in accordance with the obligations of clinical Investigators set forth in EU Clinical trials - Directive 2001/20/EC.

11.2.3 Institutional Review Board

The Investigator is responsible for the submission of the protocol, ICF, and other written materials (such as advertisements and diaries), along with relevant supporting data (e.g., IB), to the appropriate IRB for review and approval before the study can be initiated. The Investigator is also responsible for submitting amendments to the protocol and ICF to the IRB for review and approval prior to implementation of the change. The Investigator is responsible for providing the Sponsor with a letter documenting the IRB approval prior to initiation of the study or implementation of the changes, respectively.

The Investigator will not have authority to implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB of an amendment, except where necessary to eliminate an immediate hazard to study subjects. Any significant deviation from the approved protocol will be documented in the source documents and case report form (CRF).

Any deviation or change to the protocol required to eliminate an immediate hazard prior to obtaining IRB approval/favorable opinion, will be submitted as soon as possible to:

- IRB for review and approval/favorable opinion.
- The Sponsor via appropriate designees.
- Regulatory Authorities, if required by local regulations.

Documentation of IRB approval signed by the chairperson or designee of the IRB will be provided to the Sponsor via appropriate designees.

If an Amendment substantially alters the study design or increases the potential risk to the subject: (1) the ICF will be revised and submitted to the IRB for review and approval/favorable opinion; (2) the revised ICF will be used to obtain consent from subjects currently enrolled in the study if they are affected by the Amendment; and (3) the new ICF will be used to obtain consent from any new subjects prior to enrollment.

The Investigator is responsible for informing the IRB of all reportable AEs. IND Safety Reports provided by the Sponsor to the Investigator will be promptly forwarded to the IRB by the Investigator. Updates to the IB provided by the Sponsor to the Investigator will be submitted to the IRB by the Investigator.

The Investigator is also responsible for informing the IRB of the progress of the study and for obtaining annual IRB renewal. The Investigator must inform the IRB when the study is completed or terminated. After completion or termination of the study, the Investigator will submit the final clinical study report to the IRB. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995).

11.2.4 Subject Informed Consent

The Investigator must comply with informed consent regulations (21 CFR Part 50) and relevant state regulations (i.e., California Bill of Rights for California patients).

The ICF will clearly describe the nature, scope, and potential risks and benefits of the study, in a language that the subject understands. The ICF will conform to all the requirements for informed consent according to ICH GCP and US FDA guidelines (21 CFR 50) and will include any additional elements required by the Investigator's institution or local regulatory authorities. The ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Prior to the beginning of the study, the Investigator will obtain the IRB's written approval/favorable opinion of the written ICF. The IRB approved ICF will be given to each prospective participant. The subjects will be given adequate time to discuss the study with the Investigator or site staff and to decide whether or not to participate. Each subject who agrees to participate in the trial and who signs the ICF will be given a copy of the signed, dated, and witnessed document. The original signed ICF will be retained by the Investigator in the study files.

The ICF and any other information provided to subjects will be revised whenever important new information becomes available that is relevant to the subject's consent, and the Investigator will obtain the IRB's written approval/favorable opinion prior to the use of the revised documents. The Investigator, or a person designated by the Investigator, will fully inform the subject of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. Subjects will read and sign any and all revised ICFs.

11.3 Subject Confidentiality

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This is detailed in the ICF provided to the subject. An agreement for the use or disclosure of any such information (PHI) will be obtained from the subject in writing prior to performing any study-related procedures. Disclosure of subject

medical information obtained as a result of this study to third parties other than those noted below is prohibited.

Medical information resulting from a subject's participation in this study may be given to the subject's personal physician or to the appropriate medical personnel responsible for the subject's welfare. Data generated as a result of this study are to be available for inspection on request by FDA or other government regulatory agency auditors, the Sponsor (or designee), and the IRB.

The information developed in this clinical study will be used by the Sponsor in the clinical development of the IMP and therefore may be disclosed by the Sponsor as required for disclosure as a public company to other clinical investigators, to other pharmaceutical companies, to the FDA, and to other government agencies. All reports and communications relating to subjects in this study will identify each subject only by their initials and subject number.

11.4 Retention of Records

The Investigator has the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the Sponsor or designee, the IRB, and regulatory authorities (i.e., FDA or international regulatory authorities) at any time and should consist of the Essential Documents as defined in ICH E6, which include, but are not limited to, the following elements:

- Subject files, containing the completed CRFs, supporting source documentation from the medical record, including laboratory data, and the signed ICF;
- Regulatory files, containing the protocol with all amendments and Sponsor and Investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB and Sponsor; and
- Drug accountability files, including a complete account of the receipt and disposition of the IMP (active and Placebo).

The Investigator will retain all study records for at least 2 years after the last approval of a marketing application in an ICH region (i.e., United States, Europe, or Japan), and until there are no pending or contemplated marketing applications in an ICH region. If no application is filed or if the application is not approved for such indication, the Investigator will retain all study records for at least 2 years after the investigation is discontinued and regulatory authorities have been notified. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

The Investigator will notify the Sponsor prior to destroying any study records. Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor will be notified in writing in advance.

If the Investigator cannot guarantee this archiving requirement at the Investigational Site for any or all of the documents, special arrangements will be made between the Investigator and the Sponsor for storage. If source documents are required for continued care of the subject, appropriate copies for storage off site will be made.

11.5 Clinical Study Report

After completion or termination of the study, a clinical study report will be prepared. The structure and content of the report will meet that described in Structure and Content of Clinical Study Reports E3 (ICH Harmonized Tripartite Guideline, dated November 30, 1995). The Principal Investigator must verify that all information and data in the clinical study report is accurate and correct by signing the clinical study report.

12 STUDY ADMINISTRATION

12.1 Publication Policy

All information and data obtained in the course of the study are the property of the Sponsor and are considered confidential. To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts, and electronic communications), as detailed in the clinical trial agreement.

The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, HIPAA or equivalent.

12.2 Insurance

The sponsor has liability insurance at industry standard levels for a study of this size. This insurance provides coverage for damage to research subjects through injury or death caused by the study subject to the terms of the insurance policy.

12.3 Disclosure and Confidentiality

By signing the protocol, the Investigator agrees to keep all information provided by the Sponsor and Julius Clinical in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by the Sponsor and Julius Clinical (protocols, IBs, CRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by the Sponsor and Julius Clinical to the Investigator may not be disclosed to others without direct written authorization from the Sponsor and Julius Clinical, except to the extent necessary to obtain informed consent from subjects who wish to participate in the study.

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