ORAL INSULIN-INDUCED REDUCTION IN LIVER FAT CONTENT IN T2DM PATIENTS WITH NONALCOHOLIC STEATOHEPATITIS

Miriam Kidron[1], Sharon Perles[1], Reem Kaloti[2], Rami Ghantous[2], Suha F. Sanduka[2], Yasmine Malaadi[2], Rifaat Safadi[2]

[1]Oramed Pharmaceuticals, Jerusalem, Israel

[2]Institute of Gastroenterology and Liver Diseases, Hadassah University Hospital, Jerusalem, Israel

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Presenter: Miriam Kidron

Oramed Pharmaceuticals, Chief Scientific Officer

Co-author: Sharon Perles

Oramed Pharmaceuticals, VP Regulatory Affairs

Co-author: Reem Kaloti

Hadassah University Hospital, Clinical study coordinator

Co-author: Rami Ghantous

Hadassah University Hospital, Clinical study coordinator

Co-author: Suha F. Sanduka

Hadassah University Hospital, Clinical study coordinator

Co-author: Yasmine Malaadi

Hadassah University Hospital, Clinical study coordinator

Co-author: Rifaat Safadi

Hadassah University Hospital, Principal investigator

BACKGROUND

Nonalcoholic fatty liver disease (NAFLD) and subsequent nonalcoholic steatohepatitis (NASH) are leading causes of chronic liver disease.

Disease progression is tightly associated with insulin resistance and T2DM, with up to 70% of T2DM patients eventually developing NAFLD.

No safe and effective treatments currently available.

Recently, salient metabolic effects of oral insulin have been suggested, owing to first pass metabolism and local insulin availability and concentration in liver fat cells.

In light of the risk factors, pathogenesis and complications common to NAFLD/NASH and T2DM, direct insulin intervention has been suggested for T2DM patients with NAFLD.

OBJECTIVE

To assess the safety, tolerability and early effects on liver fat content of an oral insulin formulation (ORMD-0801) in T2DM patients with NASH.

METHODS

Design: Open-label

Patients: 8 adult T2DM patients with NASH

- BMI≥25
- Hepatic steatosis >8% by MRI-PDFF and CAP FibroScan ≥238 dB/m
- Liver enzyme abnormalities ULN≤5 times
- Fibrosis score 2≤F≤3
- HbA1c ≤8.5%

Treatment: 2-week placebo run-in phase, followed by 12 weeks of once-daily, preprandial oral insulin (ORMD-0801; 2x8 mg capsules)

Study visits: Baseline and after 1, 2, 4, 8 and 12 weeks of treatment

Assessments:

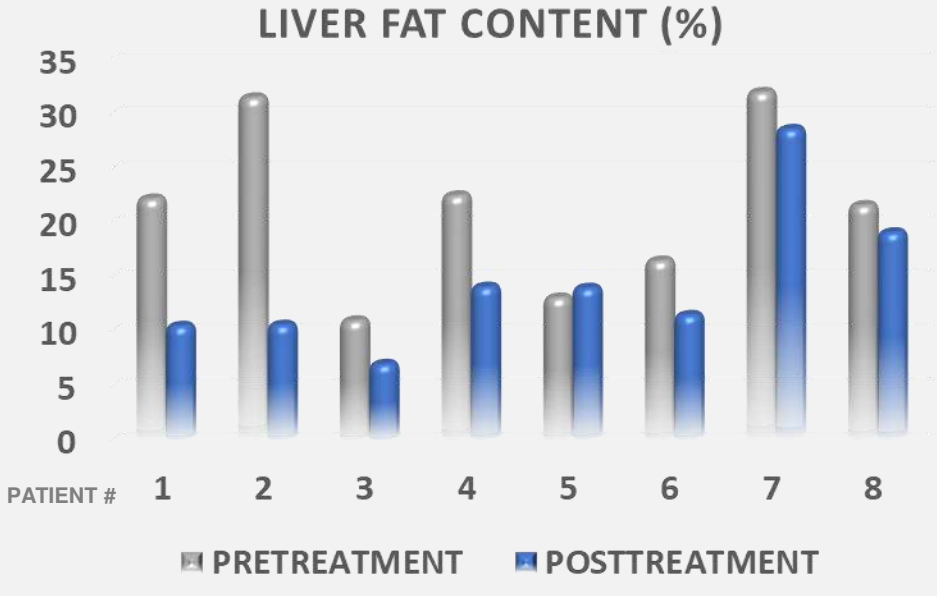
- Liver fat content: Fibroscan test and magnetic resonance imaging-proton density fat fraction (MRI-PDFF) – (*Baseline and Week 12 only*)
- Fasting blood glucose
- Fasting insulin
- Standard blood chemistry tests

RESULTS

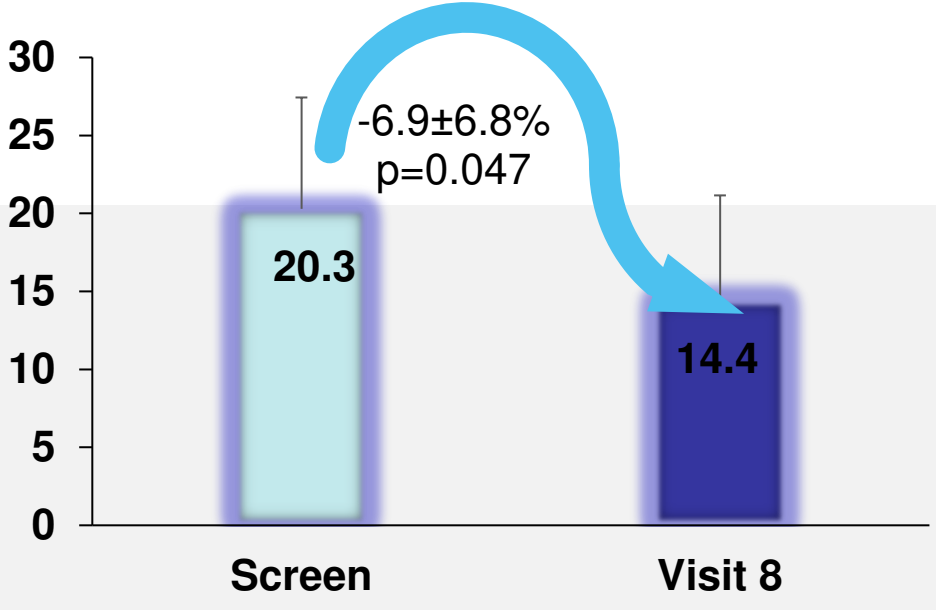
PATIENTS: 5 male, 3 female; 51.8±11.9 years; BMI: 32.8±6.0

SAFE AND TOLERABLE: No serious or severe adverse events were recorded throughout the 12-week ORMD-0801 treatment period.

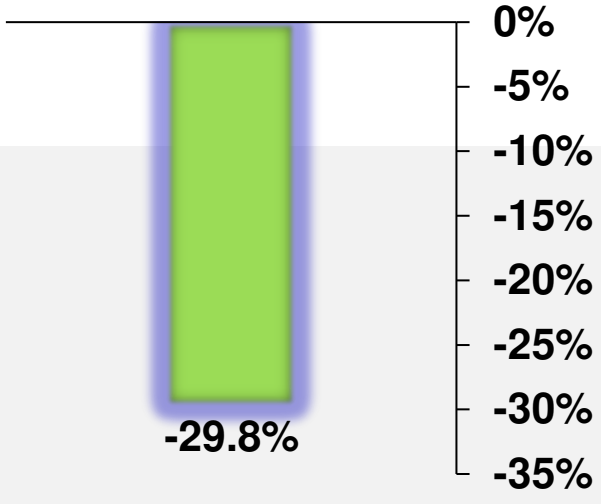
LIVER FAT REDUCTION: An observed mean reduction of -6.9±6.8% liver fat content (sign test p value: 0.035) was measured by MRI-PDFF after 12 weeks of treatment.



RESULTS – PDFF CHANGE FROM BASELINE



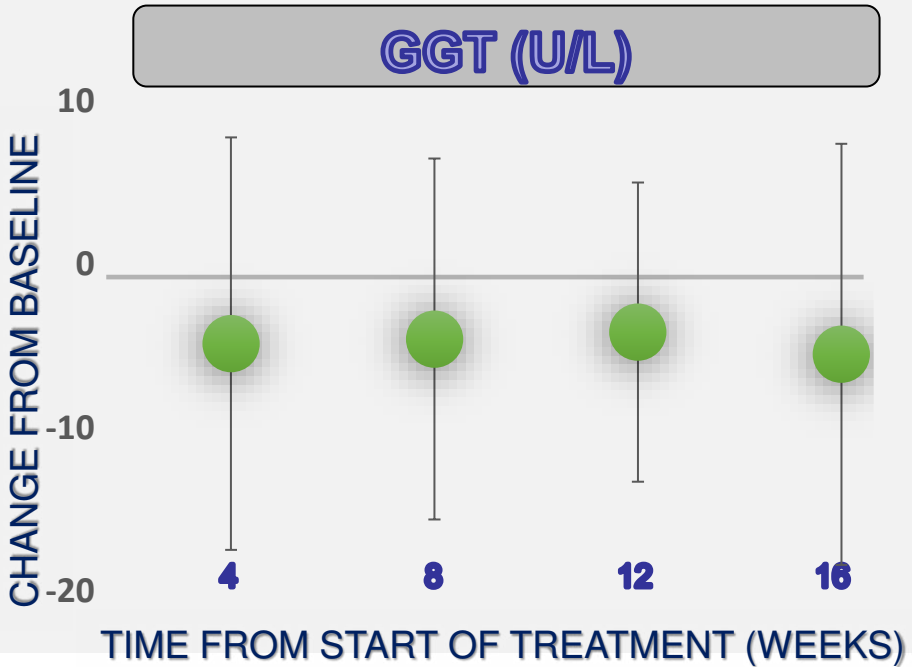
Change from Baseline

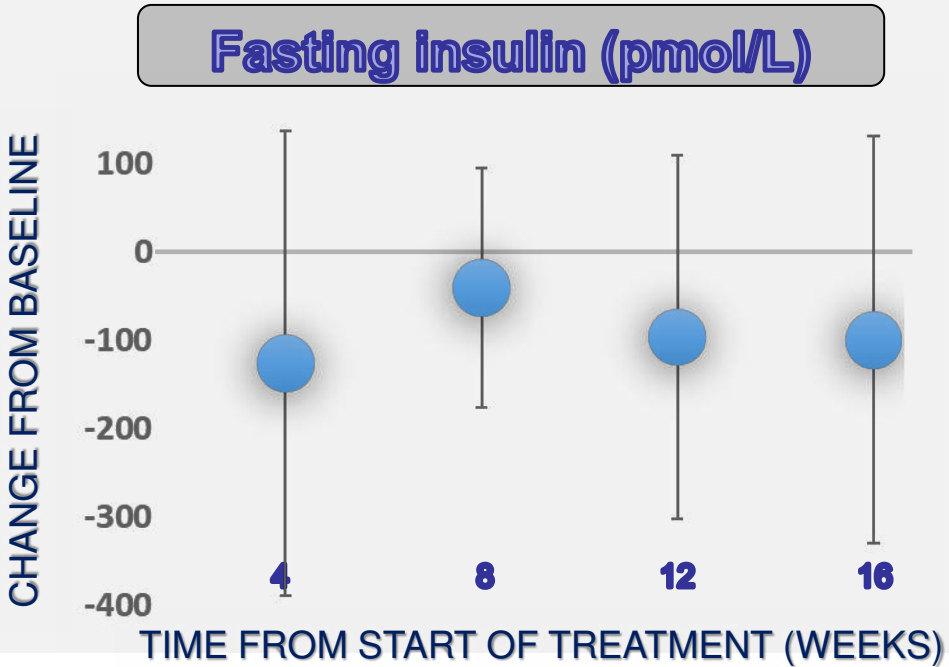


% change from Baseline

RESULTS

CHRONIC HEPATITIS MARKER: Concentrations of gamma-glutamyltransferase (GGT), a key marker of chronic hepatitis, were significantly lower after 12 weeks of treatment as compared to baseline (-14.6±13.1 U/L; sign test p value: 0.008), as were fasting insulin levels (-96.5±206.0 pmol/L; sign test p value: 0.035).





Conclusion

These preliminary observations suggest a palliative effect for oral insulin on NASH in T2DM patients, as shown by reductions in liver fat content and chronic hepatitis markers.

These encouraging findings will require further validation in large-scale, randomized clinical trials.