FINAL STUDY REPORT

PASS information

Title	Efficiency and Safety of Six Month Oglition® Therapy of Patients with Diabetes Mellitus type 2
Version identifier of the final study report	FSR-O-1
Date of last version of the final study report	11/16/2016
EU PASS register number	EUPAS13117
Active substance	Pioglitazone
Medicinal product	Oglition
Product reference	N/A
Procedure number	N/A
Marketing authorization holder(s)	Actavis
Joint PASS	No
Research question and objectives	The objective of this study was to investigate efficiency and safety of the Oglition® in therapy of diabetes mellitus type 2 in Serbia. Patient population were adults diagnosed with a DM type 2, with HbA1c values ranging from 7% to 9.5% while on monotherapy by metformin or on dual therapy by metformin and glimepiride.
Country of the study	Serbia
Author	Natasa Milic, MD, PhD milic.natasa@mayo.edu

Table of contents

1. Abstract
2. List of abbreviations
3. Investigators
4. Other responsible parties
5. Milestones
6. Rationale and background
7. Research question and objectives
8. Amendments and updates
9. Research methods
9.1. Study design
9.2. Setting
9.3. Subjects
9.4. Variables
9.5. Data sources and measurement
9.6. Bias
9.7. Study size
9.8. Data transformation
9.9. Statistical methods
9.9.1. Main summary measures
9.9.2. Main statistical methods
9.9.3. Missing values
9.9.4. Sensitivity analyses
9.9.5. Amendments to the statistical analysis plan
9.10. Quality control
10.Results
10.1. Participants
10.2. Descriptive data
10.3. Outcome data
10.4. Main results
10.5. Other analyses
10.6. Adverse events/adverse reactions
11. Discussion
11.1. Key results
11.2. Limitations
11.3. Interpretation
11.4. Generalizability
12. Other information
13. Conclusion
14. References
Appendices

1. Abstract

Title

Efficiency and Safety of Six Month Oglition® Therapy of Patients with Diabetes Mellitus type 2

Keywords

diabetes mellitus type 2, efficiency, safety, pioglitazone

Rationale and background

Pioglitazone is one of the most recently developed drugs from the class of Thiazolidinediones. It decreases glycaemia by improving peripheral utilisation of glucose and insulin sensitivity. In Serbia, pioglitazone is newly registered drug under trade the mark Oglition®. There is no evidence about its efficiency and safety in Serbian population.

Research question and objectives

The objective of this study was to determine efficiency and safety of the Oglition® in real-world clinical use for therapy of diabetes mellitus type 2 in Serbia.

Study design

This was a national multicentre prospective study performed from November 2014 to September 2015 at 5 medical centres in Serbia. Patients were monitored for 6 months while they were on therapy by Oglition®.

Subjects and study size, including dropouts

Subjects were eligible for study inclusion if they were adults diagnosed with a diabetes mellitus type 2, with HbA1c values ranging from 7% to 9.5% while on monotherapy by metformin or on dual therapy by metformin and glimepiride. Pioglitazone was added to existing therapy as a combination treatment. Available doses were 15, 30 and 45 mg.

Variables and data sources

Patients were treated with Oglition® for 6 months and monitored for main outcomes that were change of HbA1c and fasting plasma glucose during the therapy by pioglitazone, as well as occurrence of adverse and serious adverse effects.

Results

A total of 327 adult patients with diabetes mellitus type 2 with uncontrolled HbA1c were enrolled. Oglition® yielded significant decreases of HbA1c and fasting plasma glucose relative to baseline levels (0.87; $p<0.001$ and 1.89 mmol/l; $p<0.001$, respectively). Significant increases in HDL levels and decreases in triglyceride levels were also shown ($p<0.001$ for both). Safety profile of Oglition® was consistent with its known effects. There were 6 serious adverse events in this study.

Discussion

Oglition®, when added to other oral antidiabetic drugs, significantly improved HbA1c and fasting plasma glucose. Oglition® treatment also provided significant benefit with respect to plasma

HDL and triglyceride levels. Oglition® was found to be a safe and efficient addition to treatment in patients with poorly controlled diabetes.

Marketing Authorization Holder(s)

Actavis, Belgrade, Serbia

Names and affiliations of principal investigators

Nebojsa Lalic, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia

Dragan Micic, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia

Katarina Lalic, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia

Edita Stokic, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Vojvodina, Novi Sad

Mirjana Pesic, Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Nis, Nis

Aleksandar Djukic, Department for Endocrinology, Clinic for Internal Medicine, Clinical Centre of Kragujevac, Kragujevac

Teodora Beljic Zivkovic, Clinic for Endocrinology, Clinical Centre Zvezdara, Belgrade

2. List of abbreviations

AE, adverse event

ALT, alanine aminotransferase

BMI, body mass index

DM, diabetes mellitus

FPG, fasting plasma glucose

HDL, high density lipoprotein

LDL, low density lipoprotein

NYHA, New York Heart Association

OADs, oral antidiabetic drugs

SAE, serious adverse event

TG, tryclicerides

3. Investigators

Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia: Natasa Rajkovic, Ljubica Stosic, Sandra Singh, Svetlana Zoric, Goran Cvijovic, Aleksandra Kendereski,

Snezana Polovina, Danica Stamenkovic Pejkovic, Aleksandra Jotic, Tanja Milicic, Jelena Seferovic, Marija Macesic, Ljiljana Lukic, Jelena Stanarcic Gajovic

Clinic for Endocrinology, Clinical Centre Zvezdara, Belgrade: Miljanka Vuksanovic, Bogdan Buric, Marina Andjelic Jelic, Biljana Jojic, Jelena Stojanovic

Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Vojvodina, Novi Sad: Dragana Tomic Naglic, Milena Mitrovic, Jovanka Novakovic Paro, Ivana Bajkin, Dusan Tomic, Branka Kovacev Zavisic, Radoslav Pejin

Department for Endocrinology, Clinic for Internal Medicine, Clinical Centre of Kragujevac, Kragujevac: Ivana Djokic, Jelena Petrovic, Dragana Bubanja, Violeta Mladenovic

Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Nis, Nis: Radivoj Kocic, Slobodan Antic

4. Other responsible parties

N/A

5. Milestones

Milestone	Actual date
Start of data collection	November 2014
End of data collection	September 2015
Registration in the EU PASS register	April 2016
Final report of study results	November 2016

6. Rationale and background

Diabetes mellitus (DM) type 2 is the most frequent form of diabetes. Its prevalence has dramatically increased worldwide in the last three decades, mostly as the result of obesity and decreased physical activity (1). According to the fifth edition of the Atlas of International Diabetes Federation (IDF), the prevalence of diabetes in Serbia is 9.35 %, i.e. 671,000 persons has diabetes. At the same time, 771,000 people has prediabetes (1). According to the data of the Institute for Public Health "Dr Milan Jovanovic Batut" there are approximately 600,000 people having diabetes or 8.2% of population in Serbia (2).

DM type 2 is a heterogeneous group of disorders usually characterised by different degree of insulin resistance and impaired insulin secretion. Early diagnosing, and subsequent recognising of various pathogenetic processes has high therapeutic and prognostic significance. Epidemiologic studies show that DM type 2 can exist even about ten years before diagnosis, and even 50% of persons with DM type 2 has one or more complications specific for diabetes at the time of the diagnosis.

The insulin resistance is defined as the condition where the concentration of insulin in blood is higher than normally required by the level of glucose in blood (3). Insulin realises its effect by binding to insulin receptor. The tissues most sensitive to effect of insulin are liver, muscle and adipose tissue. In liver, insulin stimulates glycogenesis, synthesis of triglycerides (TG) and low density lipoproteins (LDL), and inhibits glycogenolysis, gluconeogenesis and conversion of free

fatty acids and amino acids into ketone bodies. In muscles, it induces glycogenesis and synthesis of proteins, and depositing of TG in adipose tissue.

Insulin resistance is the condition where there is an obstruction or disorder in realising the effects through insulin receptors. An increased concentration of glucose in blood provokes beta cells to even higher secretion of insulin, and there is hyperinsulinemia that provides normoglycaemia. This condition gradually develops into hyperinsulinemia and hyperglycaemia. Obesity combined with lack of activity leads to insulin resistance (3,4). Hyperinsulinemia developed as a result of insulin resistance is simultaneously the cause of numerous cardiovascular factors of risk, such as: dyslipidaemia, hypertension, impairment of blood vessels, vasoconstriction and increase of thrombocyte aggregation, on account of decreased synthesis of nitrite oxide (3,4). When insulin resistance results in exhaustion of beta cell, type 2 diabetes develops (3,4).

The goals of therapy in DM type 2 are to correct glycaemic control with values of HbA1c close to normal, but also the treatment of the conditions combined with DM type 2 (obesity, hypertension, dyslipidemia, cardiovascular disease). Current treatment of diabetes implies rapid change of therapy and combining of drugs. Pioglitazone as one of the most recent drugs in this class decreases the value of glucose in blood remedying the peripheral utilisation of glucose and insulin sensitivity. As a result of decrease of insulin resistance, the levels of circulating insulin levels are also decreasing (5,6).

Medicament therapy in DM type 2 includes individualised and sequential application of agents in 4 basic steps. In each of the steps introducing monotherapy or combination of agents is determined individually, taking into account the necessary efficiency of agent in achieving the target values of HbA1c, predisposition to hypoglycaemic episodes, changes in body weight during application of agent, main adverse effects (AE) and costs of application of therapeutic agent (7). In this respect, thiazolidindiones can be found both in the National Guide for Diagnosis and Treatment of Diabetes Mellitus from 2012, as well as in the EASD recommendations from 2012 and ADA recommendations from 2014, as the drug of second choice in combination with metformin, fully equalised in respect of efficiency with the preparations of sulphonylurea, DPP- 4 inhibitors and GLP-1 receptor agonists.

Cardioprotective effect of pioglitazone is proved by the PROactive study that was published in 2005. The results showed that application of pioglitazone in therapy reduces the incidence of CV events such as myocardial infarction by 28 % and the risk of stroke by 47 % (8). Positive effects of pioglitazone on metabolic factors of risk are equally significant and proved: decrease of fasting plasma glucose (FPG), LDL and TG in the blood, with increase of the level of HDL cholesterol. In this manner, the regulation of lipid parameters efficiently decelerates atherosclerosis (6).

On the Serbian market, the drug pioglitazone is newly registered under trademark of Oglition®. Having in mind the fact that the drug, though for years present in clinical practice worldwide, is for the first time found in the Serbian market, it is of significance to adequately and timely inform the professional public about the therapeutic aspects of pioglitazone, in order to complete, along with other peroral hypoglycaemic drugs, the therapy range designed for treatment of type 2 diabetes mellitus.

7. Research question and objectives

Primary objective was to determine efficiency and safety of the Oglition® in therapy of DM type 2 in Serbian population during the period of 6 months.

Secondary objectives were to determine efficiency and safety of the Oglition® in therapy of diabetes mellitus type 2 in Serbian population during the period of 6 months in the subgroup of patients that were: a) on the previous monotherapy by metformin, and b) on the previous dual therapy by metformin and glimepiride.

8. Amendments and updates

There were no amendments and updates for this study.

9. Research methods

9.1. Study design

This was a national multicenter prospective study.

9.2. Setting

Study was performed from November 2014 to September 2015 at 5 locations in Serbia: 1) Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Serbia, Belgrade, 2) Clinic for Endocrinology, Clinical Centre Zvezdara, Belgrade, 3) Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Vojvodina, Novi Sad, 4) Clinic for Endocrinology, Diabetes and Metabolic Diseases, Clinical Centre of Nis, Nis and 5) Department for Endocrinology, Clinic for Internal Medicine, Clinical Centre of Kragujevac, Kragujevac.

9.3. Subjects

Subjects were eligible for study inclusion if they fulfil following inclusion criteria: diagnosis of DM type 2; age > 18 years; HbA1c values ranging from 7% to 9.5% while on monotherapy by metformin (in the dose of 1 or 2 g), or on dual therapy by metformin (in dose of 1 or 2 g) and glimepiride (in dose of 2-4 g); signed patient informed consent for participation in the study (by the patients or legally acceptable representative).

Subjects were excluded based on following exclusion criteria: DM type 1; age under 18 years; hypersensitivity on active substance or any ingredient of the drug Oglition®; heart failure or patients with history of heart failure (NYHA stage I to IV); liver impairment with values of ALT > 2.5 times higher than normal values; diabetic ketoacidosis; patients on dialysis; malignity of any localisation; pregnancy or breast-feeding; blood in urine; carcinoma of urinary bladder; positive family anamnesis for carcinoma of urinary bladder; myocardial infarction in previous 6 months; stroke in previous 6 months; osteoporotic fracture in previous 2 years; simultaneous participation in another research.

9.4. Variables

Exposure: Patients were treated with Oglition® for 6 months and monitored, according to following plan of visits:

Visit I: Introducing the patients with therapy. Oglition® was added in 15 mg dose to existing therapy as a combination treatment.

Visit II: after 3 months (12 weeks) – control of HbA1c and FPG level. Available doses were 15, 30 and 45 mg.

Visit III: after 6 months (24 weeks) – final control of HbA1c and FPG. Available doses were 15, 30 and 45 mg.

Outcomes: Main outcomes were:

- Change of HbA_1c level during the therapy by Oglition®
- Change of FPG level during the therapy by Oglition®
- Occurrence of adverse events (AE) and serious adverse events (SAE) during the therapy by Oglition®

Data collection: The following data were collected for introducing Oglition® (visit 1):

- date of examination,
- patient's initials,
- demographic data: age; sex; height; weight, waist,
- history of diabetes,
- glycaemic status (FPG, HbA1c),
- lipid status,
- complications of diabetes and associated diseases,
- Oglition® therapy (recommended dose 15 mg), and
- concomitant therapy with other drugs.

The following data were collected for monitoring of Oglition® therapy (visit 2, after 12 weeks):

- date of examination,
- glycaemic status (FPG, HbA1c),
- Oglition® therapy (recommended dose),
- adverse effects, serious adverse effects, and
- concomitant therapy with other drugs.

The following data were collected for monitoring of Oglition® therapy (visit 3, after 24 weeks)

- date of examination,
- glycaemic status (FPG, HbA1c),
- lipid status,
- weight, waist circumference,
- Oglition® therapy (recommended dose),
- adverse effects, serious adverse effects, and
- satisfaction of physicians with Oglition® therapy.

9.5. Data sources and measurement

Procedures conducted on visits were the same that are used in a regular clinical practice for the patients with diabetes. The blood and urine laboratory results were done in local laboratories by the means of usual clinical practice.

Data were collected using predefined Questionnaire prepared for the purpose of this study (Annex 1).

Pharmacovigilance definitions:

An undesirable event (Adverse Event - AE) was defined as an undesirable experience which occurred in the period of application of the drug and for which the cause-effect connection with application of the drug Oglition® need not be proved. An undesirable experience was defined as any unintended and undesirable sign connected in terms of time with application of the drug Oglition®, such as:

- abnormal laboratory findings,
- new disease,
- worsening of signs or symptoms of disease that we are treating or certain simultaneous diseases,
- effect of other drugs that the patient is simultaneously taking, unconnected with participation in this study, or
- combination of one or more of the listed factors.

Serious undesirable event (Serious Adverse Event - SAE) was defined as the undesirable event which results in:

- death,
- direct life jeopardy,
- permanent or severe impairment, i.e. disability,
- hospital treatment or prolongation of the existing hospital treatment,
- congenital anomalies, i.e. a defect detected upon birth, or
- other medically significant condition.

9.6. Bias

Patients were recruited in consecutive manner to address potential sources of bias.

9.7. Study size

The sample size calculation is based on the estimate of 95% confidence interval for frequency of patients with achieved target value of HbA1c (HbA1c≤7) after the treatment. With assumption that ≥ 30% patients would be after the treatment within the reference values of HbA1c, the number of patients which should be included in the study is 323, with selected precision of 5.0% and an alpha error of 0.05.

9.8. Data transformation

There was no data transformation applied in this study.

9.9. Statistical methods

9.9.1. Main summary measures

The glycaemia and HbA1c levels are presented as mean values with standard deviation as a measure of variability, while the reported hypoglycaemic episodes and other adverse events are expressed by absolute numbers with percentages. Other examined characteristics are presented as mean value ± sd or median with interquartile range, or as absolute frequencies with percentages, where appropriate.

9.9.2. Main statistical methods

Data distribution was assessed by Kolmogorov-Smirnov test. Changes in glycaemia and HbA1c levels from baseline to the 3 and 6 months of therapy were evaluated by Repeated Measures ANOVA. Student's t test for paired samples was used for the assessment of weight and waist change from baseline to the 6 months, while Wilcoxon test was used for determining holesterol, HDL and tryclicerides change from baseline to the 6 months.

9.9.3. Missing values

No missing values replacements were done.

9.9.4. Sensitivity analyses

In order to consider the secondary goal of the study, changes in values of glycaemia and HbA1c from the initial value to the value after 6 and 12 months were also assessed in the subgroup of patients on the previous monotherapy by metformin, and in the subgroup of patients on the previous dual therapy by metformin and glimepiride.

9.9.5. Amendments to the statistical analysis plan

There were no amendments to the statistical analysis plan.

9.10. Quality control

All measurements in different centers and different laboratories were done in a predefined uniform and standardized way. Each center and laboratory fulfilled standards and had internal and external quality control defined by national principles of good practices. No additional quality control for laboratory analysis was done by the sponsor of the study. Database with research data was checked to ensure that data gathered from different data sources is clean, accurate and in a standard format. User input for consistency with a minimum/maximum range were examined by simple range validation, while consistency with a test for evaluating a sequence of characters were examined by constraint validation, such as one or more tests against regular expressions. Structured validation was done for the combination of any of various basic data type validation steps, along with more complex processing. For random sample of 5% patients all data were checked for consistency with original inputs.

10. Results

10.1. Participants

Studied population included 327 participants. All patients (n=327) fulfilled inclusion criteria, and none of the patients had any of the exclusion criteria.

10.2. Descriptive data

There were 165 men (52.5%) and 149 (47.5%) women in studied population; with mean age of 59.4±9.6 yrs, and median disease duration of 79 months (range 3-360). Baseline demographic characteristics of studied population is given in Table 1.

Table 1. Baseline demographic characteristics of studied population

Variable	**x±sd (min-max)**
n	327
Age, yrs	59.4±9.6 (28-78)
Male, n (%)	146 (44.9%)
BMI, kg/m^2	30.9±5.5 (20.2-53.5)
Weight, kg	88.2±18.2 (47-170)
Waist, cm	102.3±14.0 (45-150)
DM duration, months*	79 (3-360)

* presented as median (min-max)
BMI, body mass index; DM, diabetes mellitus

DM complications had 87 (26.6%) participants (Figure 1). Diabetic neuropathy was the most common DM complication, registered in 16.5% of participants. Frequency of all DM complications presented in the study population is shown in Figure 2.

Figure 1. DM complications in studied population

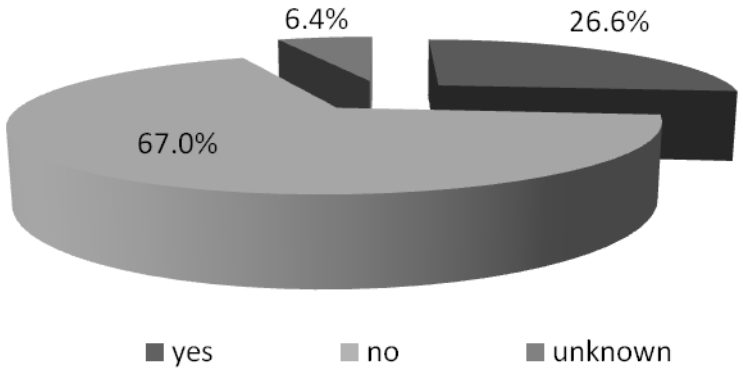
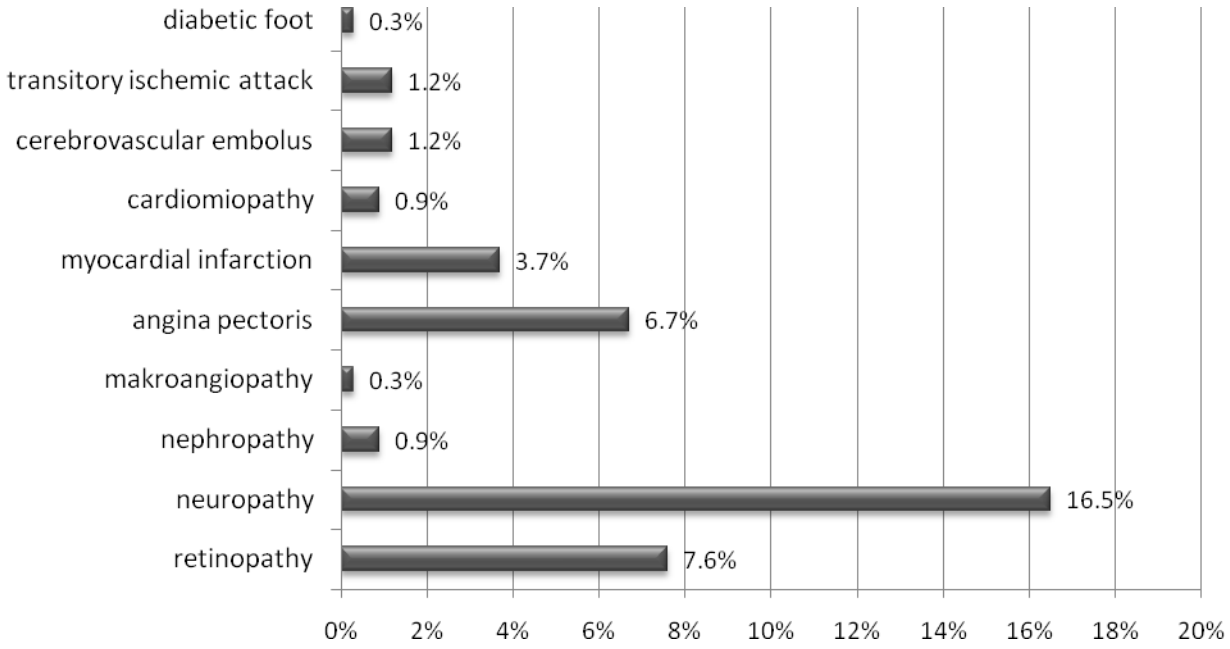


Figure 2. Distribution of DM complications in the studied population



At least one concomitant disease had 83.4% of participants. Most common was hypertension (65.4%), followed by dyslipidemia (55.7%) (Table 2).

Table 2. Concomitant diseases in studied population

Variable	**n (%)**
Concomitant disease	
yes	272 (83.4%)
unknown	2 (0.6%)
Hypertension	214 (65.4%)
Dyslipidemia	182 (55.7%)

At study entry 148 (45.3%) of patients were on monotherapy by metformin and 179 (54.7%) patients were on dual therapy by metformin and glimepiride. Distribution of patients according to daily dose of Metformin and Glimepiride is presented in Table 3.

Table 3. DM therapy at study entry (baseline study visit)

Therapy	**n (%)**
Metformin	327 (100%)
1000 mg	18 (5.5%)
2000 mg	307 (93.8%)
Unknown	2 (0.6%)
Median dose (min-max)	2000 (1000-2000)
Glimepiride	179 (54.7%)
2 mg	56 (17.1%)
3 mg	38 (11.6%)
4 mg	85 (26.0%)
Median dose (min-max)	3 (2-4)

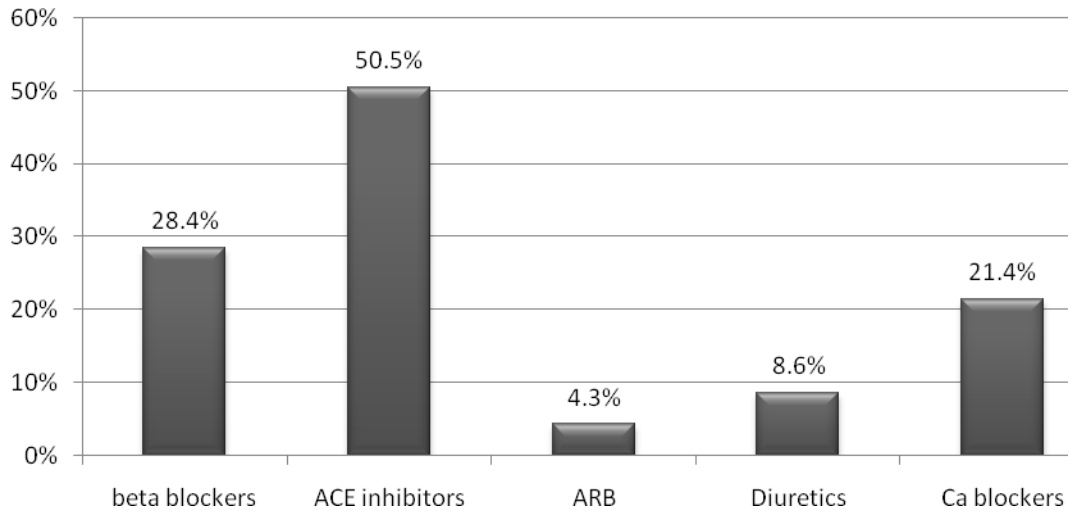
Most common concomitant therapy were antihypertensive therapy (62.1%) and therapy for dislipidemia (53.8%). Distribution of patients according to use of concomitant therapy is presented in Table 4. Distribution of studied population according to use of antihypertensive drugs is shown in Figure 3.

Table 4. Concomitant therapy in studied population

Concomitant therapy	**n (%)**
Antihypertensive drugs	
Beta blockers	93 (28.4%)
ACE inhibitors	165 (50.5%)
ARB	14 (4.3%)
Diuretics	28 (8.6%)
Ca blockers	70 (21.4%)
Number of antihypertensive drugs	
1	77 (23.5%)
2	100 (30.6%)
3	16 (4.9%)
>3	9 (2.8%)
Dislipidemia therapy	
Statins	116 (35.5%)
Fibrats	35 (10.7%)

ARB, Angiotenzin II receptors antagonist

Figure 3. Distribution of studied population according to use of antihypertensive drugs

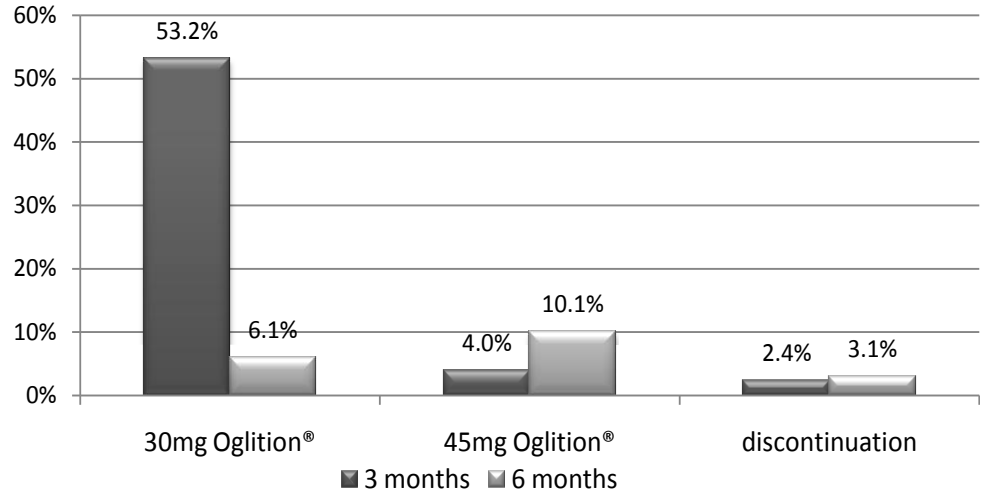


Starting dose (at baseline visit) for all patients was 15 mg of Oglition®. At first control visit, 196 (59.9%) patients changed Oglition dose; for 174 (53.2%) dose was increased to 30 mg, while for 13 (4.0%) it was increased to 45 mg (Figure 4). For 8 (2.4%) patients Oglition® was discontinued. Changes for metformin and glimepiride therapy was recorded in 3.4%, which included dose reduction. Reduction for metformin happened in 3 (0,9%) patients and for glimepiride in 8 (2.4%) patients.

At final visit 19,3% patients changed Oglition® dose. For 6.1% it was increased to 30 mg, and for 10.1% to 45 mg (Figure 4). For 10 (3.1%) patients Oglition® was discontinued at this study visit. Changes in metformin therapy were not recorded at this study visit, while an dose decrease for glimepiride happened in 5.2% participants. In 3.7% patients there was a change instatine/fibrate dose (3.4% for statins, and 0.6% for fibrates).

In total, Oglition® therapy was discontinued in 18 (5.5%) patients in this study.

Figure 4. Recommended Oglition® doses in studied population



10.3. Outcome data

There was a statistically significant decrease in weight throughout the study duration (p<0.001) (Table 5 and Figure 5). Decrease in waist were also recorded throughout the study duration (p<0.001) (Table 5 and Figure 6).

Table 5. Changes in anthropometric parameters during the study visits

Variable	**x±sd (min-max)**	**Mean difference (95% CI)**	**p**
Weight, kg			
Baseline	88.5±17.9(47-170)	0.6 (0.3-0.9)	<0.001
At 6 months	87.9±17.6(46-171)		
Waist, cm			
Baseline	103.0±13.2(66-145)	0.7 (0.4-1.0)	<0.001
At 6 months	102.2±13.1(64-145)		

Figure 5. Weight change during the study period

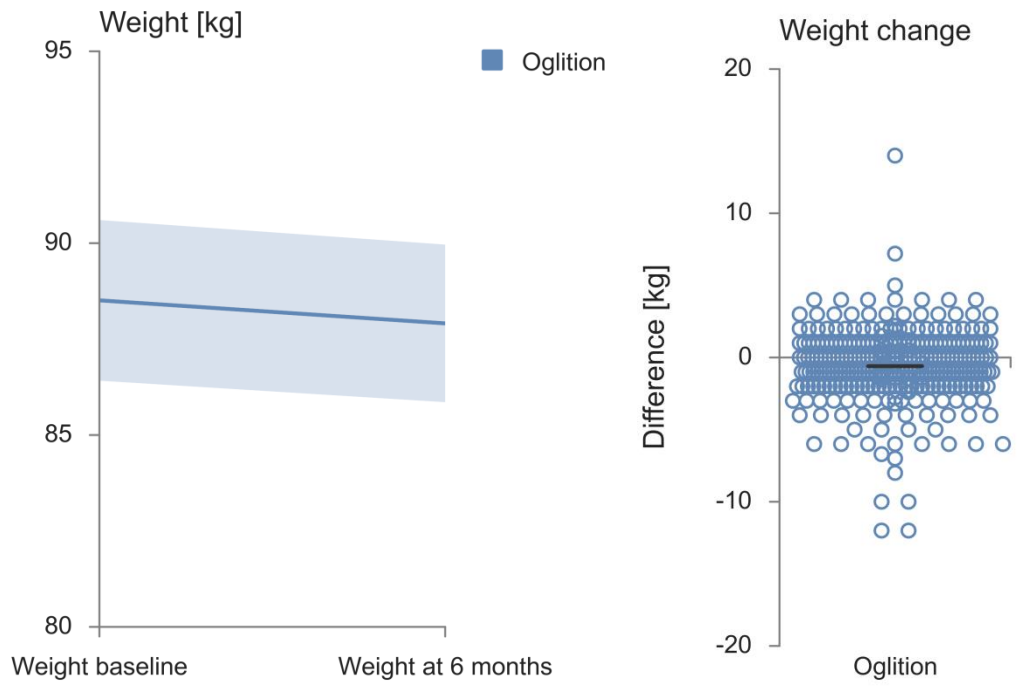
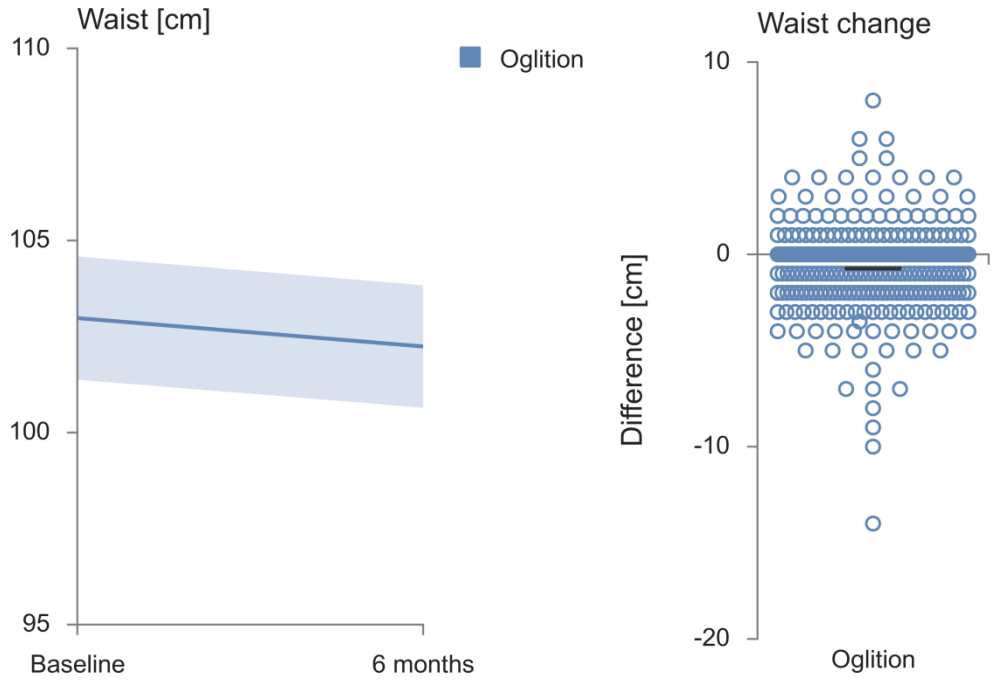


Figure 6. Waist change during the study period



There was a statistically significant decrease in cholesterol levels throughout the study duration (p<0.001) (Table 6 and Figure 7). Decrease in triglycerides levels were also recorded throughout the study duration (p<0.001) (Table 6 and Figure 8), while HDL increased significantly (Table 6 and Figure 9). There was no change in LDL levels (p=0.337) (Table 6).

Table 6. Changes in lipid levels during the study visits

Variable	Med (min-max)	p
Cholesterol, mmol/L		
Baseline	5.4 (2.8-11.0)	<0.001
At 6 months	5.3 (1.6-9.8)	
LDL, mmol/L		
Baseline	3.3 (1.1-7.3)	0.337
At 6 months	3.3 (1.3-8.7)	
HDL, mmol/L		
Baseline	1.1 (0.4-9.8)	<0.001
At 6 months	1.2 (0.6-11.4)	
TG, mmol/L		
Baseline	1.9 (0.5-22.5)	<0.001
At 6 months	1.7 (0.6-9.0)	

Figure 7. Cholesterol change during the study period

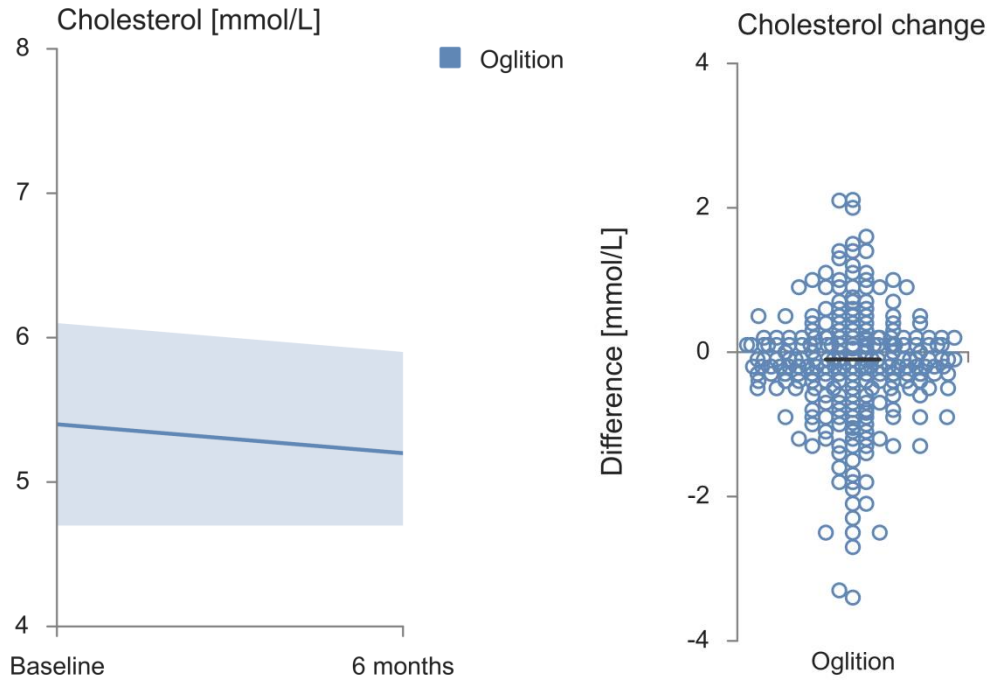


Figure 8. Triglycerides change during the study period

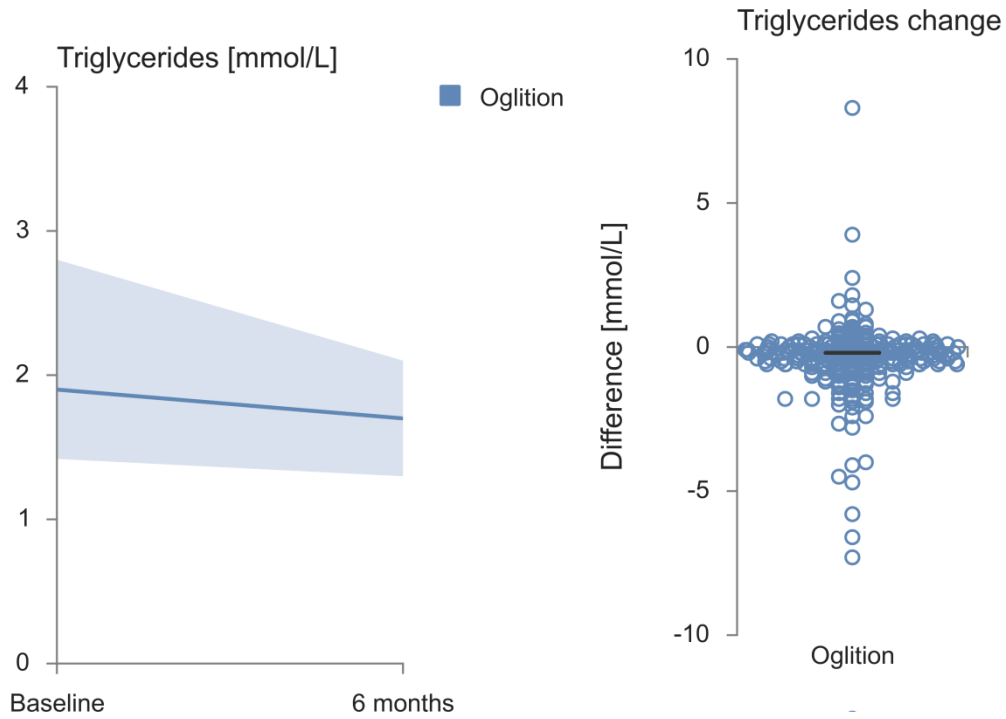
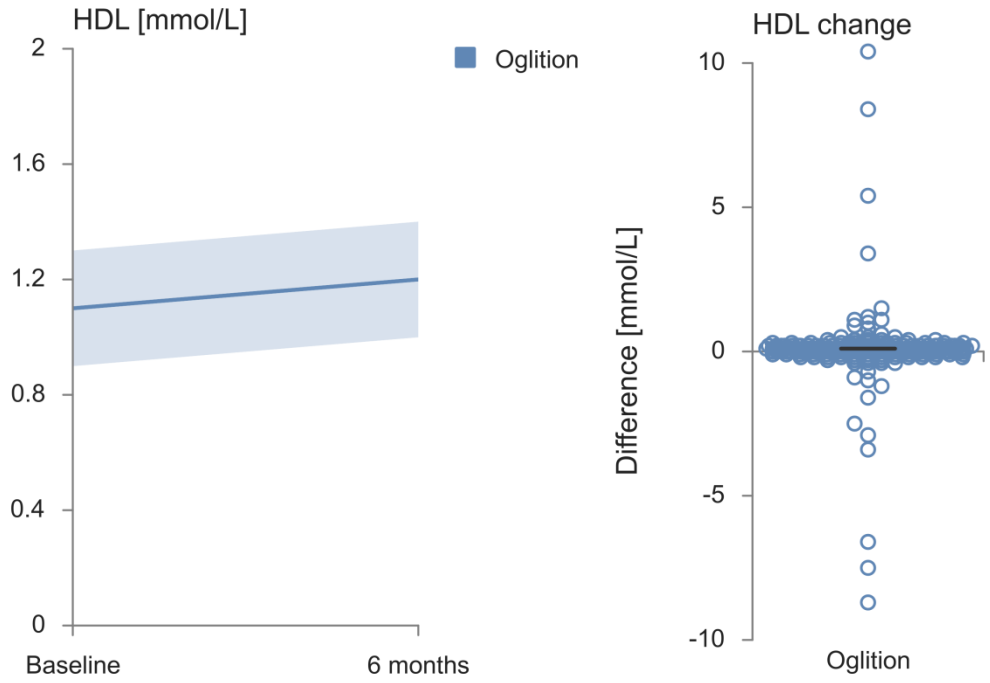


Figure 9. HDL change during the study period



10.4. Main results

There was a statistically significant decrease in glucose levels throughout the study duration (p<0.001). Glucose levels decreased significantly from baseline visit to 3 months of follow up, as well as from 3 months to 6 months follow up (Table 7 and Figure 13). Decrease in levels of HbA1c were also recorded throughout the study duration (p<0.001). HbA1c levels decreased significantly from baseline visit to 3 months of follow up, as well as from 3 months to 6 months follow up (Table 7 and Figure 10). Target value of HbA1c (HbA1c≤7) achieved 165 (50.5%; 95%CI 45.0-55.9%) patients after the 6 months treatment with Oglition.

Table 7. Changes in glucose and HbA1c% levels during the study visits

Variable	**x±sd (min-max)**	**p**	**Mean difference (95% confidence interval)**	**p post chock**
Glucose, mmol/L				
Baseline	9.2±2.3 (1.3-16.0)	<0.001	Baseline vs 3 months 1.2 (1.0-1.4)	<0.001
At 3 months	8.0±1.8 (3.9-15.1)		3 vs 6 months 0.7 (0.5-0.9)	<0.001
At 6 months	7.3±1.7 (4.0-14.9)		Baseline vs 6 months 1.9 (1.7-2.1)	<0.001
HbA1c%				
Baseline	8.1±0.7 (7.0-10.0)	<0.001	Baseline vs 3 months 0.6 (0.5-0.7)	<0.001
At 3 months	7.5±0.8 (5.5-10.2)		3 vs 6 months 0.3 (0.2-0.4)	<0.001
At 6 months	7.2±0.8 (5.2-11.3)		Baseline vs 6 months 0.9 (0.8-1.0)	<0.001

Figure 10. Changes in glucose levels during the study visits

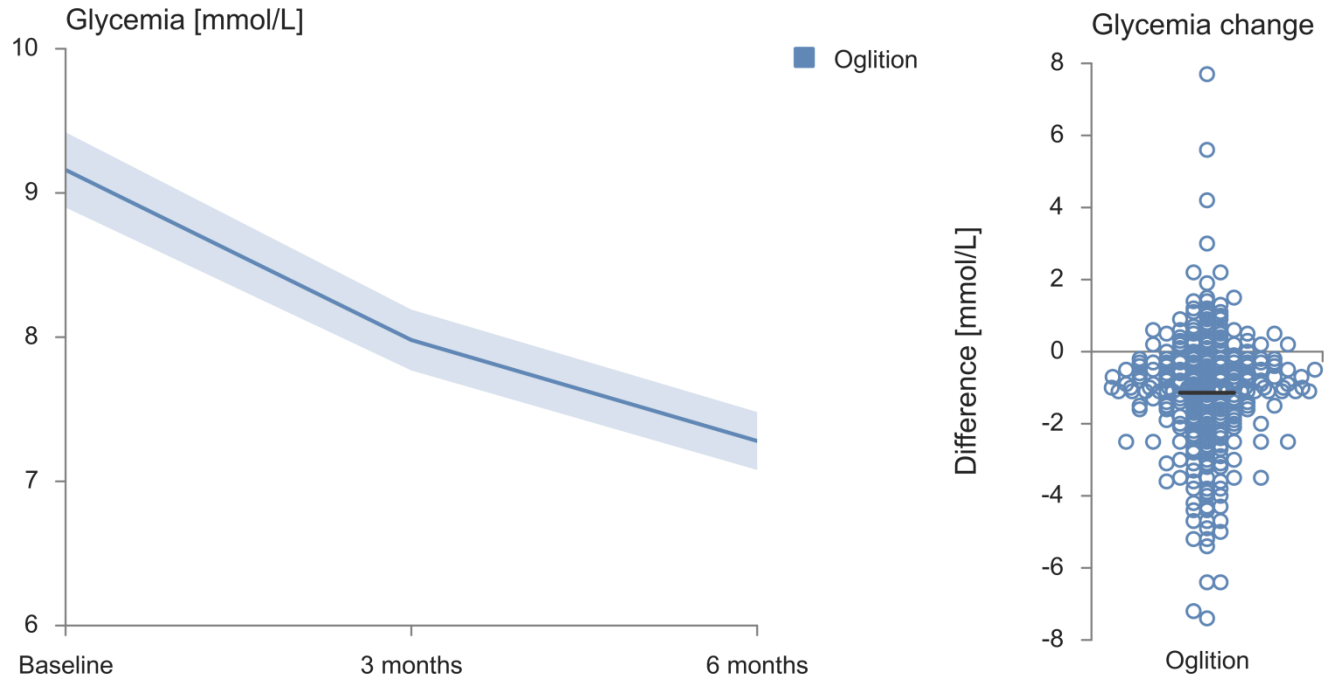
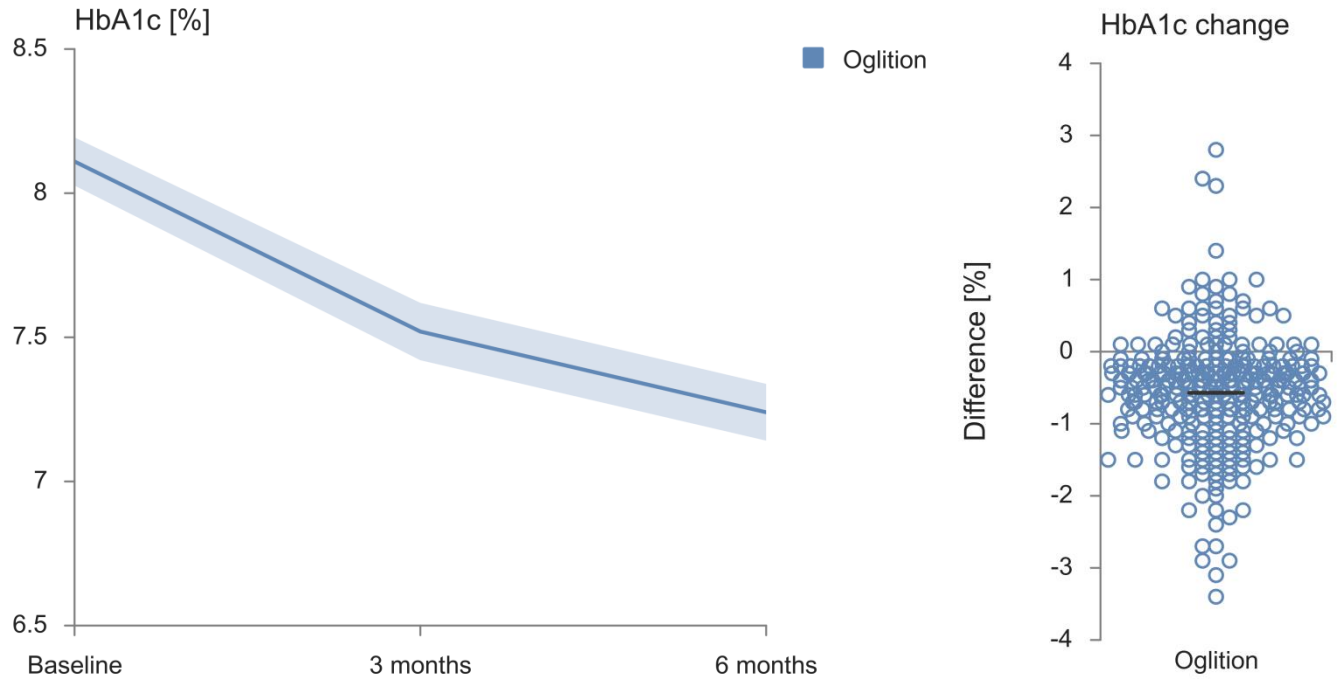


Figure 11. Changes in HbA1c% levels during the study visits



Changes in HbA1c% and FPG according to other oral antidiabetic drugs (OADs) used in the study i.e. previous monotherapy vs. dual therapy are shown in Tables 8 and 9. There was a statistically significant decrease in HbA1c and FPG throughout the study duration in both groups (p<0.001 for all time points in both groups).

Table 8. Changes in glucose levels according to other OADs used in the study

Variable	**x±sd (min-max)**	**p**	**Mean difference (95% confidence interval)**	**p post chock**
Oglition+Metformin				
Baseline	8.4±1.8 (1.3-16.0)	<0.001	Baseline vs 3 months 1.1 (0.9-1.4)	<0.001
At 3 months	7.3±1.3 (3.9-15.1)		3 vs 6 months 0.6 (0.4-0.7)	<0.001
At 6 months	6.7±1.2 (4.0-14.9)		Baseline vs 6 months 1.7 (1.4-1.9)	<0.001
Oglition+Metformin+ Glimepirid				
Baseline	9.8±2.4 (7.0-10.0)	<0.001	Baseline vs 3 months 1.2 (0.9-1.5)	<0.001
At 3 months	8.5±2.0 (5.5-10.2)		3 vs 6 months 0.8 (0.6-1.1)	<0.001
At 6 months	7.7±1.9 (5.2-11.3)		Baseline vs 6 months 2.1 (1.7-2.4)	<0.001

Table 9. Changes in HbA1c% levels according to other OADs used in the study

Variable	**x±sd (min-max)**	**p**	**Mean difference (95% confidence interval)**	**p post chock**
Oglition+Metformin				
Baseline	7.8±0.7 (1.3-16.0)	<0.001	Baseline vs 3 months 0.6 (0.4-0.7)	<0.001
At 3 months	7.3±0.7 (3.9-15.1)		3 vs 6 months 0.3 (0.2-0.4)	<0.001
At 6 months	7.0±0.7 (4.0-14.9)		Baseline vs 6 months 0.8 (0.7-1.0)	<0.001
Oglition+Metformin+ Glimepirid				
Baseline	8.3±0.7 (7.0-10.0)	<0.001	Baseline vs 3 months 0.6 (0.5-0.7)	<0.001
At 3 months	7.7±0.9 (5.5-10.2)		3 vs 6 months 0.3 (0.2-0.4)	<0.001
At 6 months	7.4±0.9 (5.2-11.3)		Baseline vs 6 months 0.9 (0.7-1.0)	<0.001

10.5. Other analyses

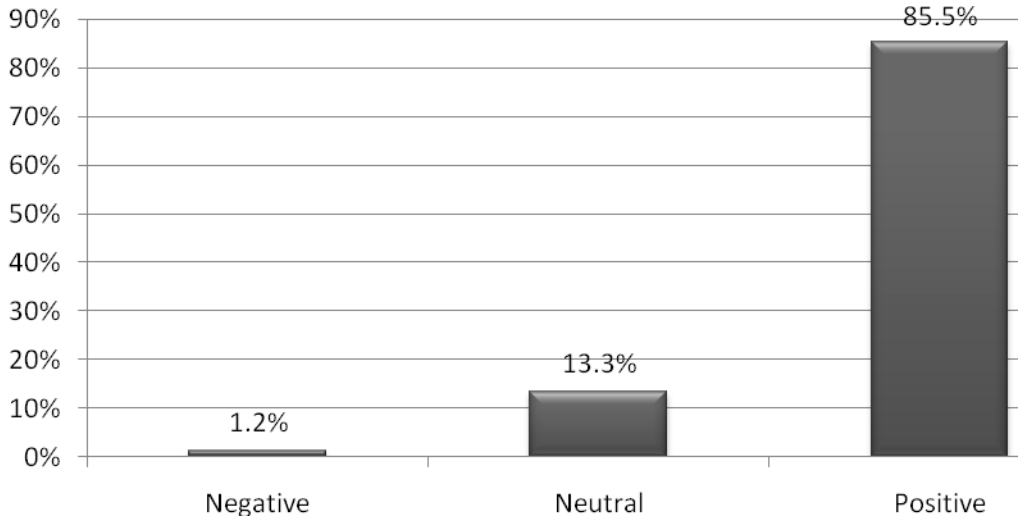
Two thirds (66.7%) of physicians showed positive attitudes regarding efficacy of Oglition® therapy (Table 10). 73.7% of physicians concluded that Oglition® therapy was well tolerated, and 65.7% of them would continue this therapy for their patients. Distribution of physicians according to their satisfaction with Oglition® efficiency is given in Figure 12.

Table 10. Distribution of physicians according to their satisfaction with Oglition therapy

Variable	**n (%)**
*Attitude regarding efficacy**	
Negative	3 (1.2%)
Neutral	34 (13.3%)
Positive	218 (85.5%)
*Attitude regarding safety***	
Negative	/
Neutral	13 (5.1%)
Positive	241 (94.9%)
*Would continue therapy****	215 (89.2%)

* 72 physicians didn't answer
** 73 physicians didn't answer
***86 physicians didn't answer

Figure12. Distribution of physicians according to their satisfaction with Oglition® efficiency



10.6. Adverse events/adverse reactions

Adverse events were recorded in 21 (6.4%) patients, out of which 6 (1.8%) were characterized as having serious adverse events. All adverse events recorded in studied population are presented in Table 11.

Table 11. Adverse events and serious adverse events in studied population

SAE	AE	Expected	Metformin	Glimepiride	Concomitant therapy	Resolved	Quit study
no	Weight gain	yes	2 g	3 mg	Ramipril; Diltiazem; Aspirin; Simvastatin	/	yes
yes	Blood in the stool	no	4 g	/	/	/	yes
no	Cough	no	2 g	/	/	yes	yes
yes	Hypertension; Stifling; Weight gain	no; yes; yes	2 g	4 mg	Fosinopril; Amlodipin; Bisoprolol; Aspirin; Rosuvastatin	yes	no
yes	Hypertension; Breath shortness	no; yes	2 g	2 mg	/	yes	yes
no	Nausea; Itching; Pain under the rib	yes; no; no	2 g	3 mg	/	/	yes
yes	Stifling	yes	2 g	2 mg	Metoprolol; Ramipril	yes	yes
yes	Stifling; Hypertension; Exhaustion; Headache	yes; no; yes; yes	2 g	2 mg	Enalapril; Verapamil	yes	yes
no	Diarrhea	no	1 g	/	/	yes	yes
ne	Headache; Vertigo; Stomach pain; Weight gain	yes; yes; yes	2 g	2 mg	Ramipril	yes	no
yes	Erectile dysfunction	yes	1 g	/	Fosinopril; Hidrohlortiazid	yes	yes
no	Weight gain, Weight loss	yes; no	2 g	4 mg	Enalapril	yes	no
no	Taste loss; Weight loss	no; no	2 g	/	Metoprolol; Fosinopril; Aspirin; Atorvastatin	/	yes
no	Hypoglycemia	yes	2 g	4 mg	Ramipril; Aspirin; Nebivolol; Atorvastatin	yes	no
no	Headache	yes	2 g	/	/	yes	no
no	Headache	yes	2 g	/	/	yes	no
no	Headache	yes	2 g	/	/	yes	no
no	Headache	yes	2 g	/	/	yes	no
no	Headache	yes	2 g	/	/	yes	no
no	Headache	yes	2 g	/	/	yes	no
no	Headache	yes	2 g	/	/	yes	no

11. Discussion

11.1. Key results

A total of 327 adult patients with DM type 2 with uncontrolled HbA1c were enrolled. Oglition® yielded significant decreases of HbA1c and FPG relative to baseline levels (0.87; $p<0.001$ and 1.89 mmol/l; $p<0.001$, respectively). Significant increases in HDL levels and decreases in TG levels were also shown ($p<0.001$ for both). Safety profile of Oglition® was consistent with its known effects. There were 6 serious adverse events in this study.

11.2. Limitations

This study has some limitations, including the lack of control group, and a relatively short period of observation (6 months). However, study findings concerning efficiency and safety parameters seem to be in accordance with other studies.

11.3. Interpretation

The goal of many clinicians who manage diabetes is to achieve optimum glucose control alongside weight loss and a minimum number of hypoglycemic episodes. Addition of Oglition® to other OADs achieved this goal. Acceptable safety profile for Oglition® was observed.

11.4. Generalizability

Oglition® was found to be a safe and efficient addition to treatment in patients with poorly controlled diabetes.

12. Other information

There is no other information for this study.

13. Conclusion

Oglition®, when added to other OADs, significantly improved HbA1c and FPG. Oglition® treatment also provided significant benefit with respect to plasma HDL and TG levels. Oglition® was found to be a safe and efficient addition to treatment in patients with poorly controlled diabetes.

14. References

1. Harrison's Principles of Internal Medicine, 15th edition.

2. Institute for Public Health "Dr Milan Jovanovic Batut", November 2011.

3. Zimmet P. Addressing the insulin resistance syndrome: a role for the thiazolidinediones. Trends Cardiovasc Med. 2002;12(8):354-62.

4. Hamburg HM et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. Atheroscler Throm Vasc Biol. 2007;27:2650-6.

5. Bell D. Treatment of Type 2 Diabetes with a Combination of Two Insulin Sensitizers – Increased Efficaccy and Fewer Side-effects. US Cardiology. 2004;1(1):29-33.

6. Cheng AY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ. 2005; 172(2):213-26.

7. National Guide of Good Clinical Practice for Diagnosis and Treatment of Diabetes Mellitus.

8. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefèbvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Korányi L, Laakso M, Mokán M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005;366(9493):1279-89.

9. Pastromas S, Koulouris S. Thiazolidinediones: antidiabetic drugs with cardiovascular effects. Hellenic J Cardiol. 2006;47(6):352-60.

10. DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, Clement SC, Henry RR, Hodis HN, Kitabchi AE, Mack WJ, Mudaliar S, Ratner RE, Williams K, Stentz FB, Musi N, Reaven PD; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med. 2011;364(12):1104-15.

Appendices

OBRAZAC ZA PRIKUPLJANJE PODATAKA

V I Z I T A 1

Datum posete: I__I__I I__I__I I__I__I__I__I Broj pacijenta: I__I__I
dan mesec godina

Demografski i antropometrijski podaci

Inicijali bolesnika: I__I__I__I Starost: I__I__I Pol: ❑M ❑ Ž
(godine)

Visina : I__I__I__I (cm)

Težina : I__I__I__I (kg)

Obim struka I__I__I__I (cm)

KRITERIJUMI UKLJUČIVANJA

Kriterijumi za uključivanje

- Dijagnoza DM tip 2 ❑ DA ❑ NE
- Starost > 18 godina❑DA ❑ NE
- Pacijenti sa HbA1c vrednostima od 7% -9,5% na terapiji metforminom (monoterapija) u dozi od 1 ili 2 gr ili metforminom u dozi 1 ili 2 gr i glimepiridom 2-4 gr (dvojna terapija)

❑ DA❑ NE

- Potpisan informisani potpisak pacijenta za učešće u studiji (od strane bolesnika ili zakonski prihvatljivog zastupnika

❑ DA❑ NE

KRITERIJUMI NEUKLJUČIVANJA

Starost : ispod 18 godina ❑ DA ❑ NE

Preosetljivost na aktivnu supstancu ili bilo koji sastojak leka Oglition®

❑ DA❑ NE

Srčana insuficijencija ili pacijenti sa istorijom srčane insuficijencije (NYHA stadijumi I do IV)

❑ DA❑ NE

Oštećenje jetre sa vrednostima enzima jetre ALT> 2,5 puta iznad normalnih vrednosti

❑ DA❑ NE

Dijabetesna ketoacidoza❑DA ❑ NE

Pacijenti na dijalizi❑DA ❑ NE

Malignitet bilo koje lokalizacije ❑ DA ❑ NE

Trudnoća ili dojenje❑DA ❑ NE

Krv u mokraći❑DA ❑ NE

Karcinom mokraćne bešike❑DA ❑ NE

Pozitivna porodična anamneza na karcinom bešike

❑ DA❑ NE

Infakrkt miokarda u prethodnih 6 meseci

❑ DA❑ NE

Moždani udar u prethodnih 6 meseci

❑ DA❑ NE

Osteoporotični prelomi u prethodne 2 godine

❑ DA❑ NE

Istovremeno učešće u drugom istraživanju

❑ DA❑ NE

Istorija šećerne bolesti

Trajanje dijabetesa: I__I__I g I__I__I m

Glikemijski status

Upišite vrednosti i datum nalaza

Glukoza našte I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I

dan mesec godina

HbA1c I__I__I, I__I % Datum I__I__I I__I__I I__I__I__I

dan mesec godina

Lipidni status

Upišite vrednosti i datum nalaza

Ukupni holesterol I__I__I, I__I mmol/l Datum I__I__I I__I__I I__I__I__I

dan mesec godina

LDL Holesterol I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I

dan mesec godina

HDL Holesterol I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I

dan mesec godina

Trigliceridi I__I__I, I__I mmol/L Datum I__I__I I__I__II__I__I__I

dan mesec godina

Kasne dijabetesnekomplikacije i pridružena oboljenja

Ima li bolesnik neku od navedenih komplikacija?

❑ DA❑ NE❑Nije poznato

Ako je odgovor DA obeležite vrstu dijabetesne komplikacije:

Kasne dijabetesne komplikacije:

- ❑ Dijabetesna retinopatija
- ❑Dijabetesna neuropatija
- ❑Dijabetesna nefropatija
- ❑Dijabetesna makroangiopatija
- ❑ Angina pectoris
- ❑ Infarkt miokarda
- ❑ Dijabetesna kardiomiopatija
- ❑ Cerebrovaskularna embolija
- ❑Tranzitorni ishemički atak
- ❑Dijabetesno stopalo
- ❑Druga vaskularna oboljenja, koja :_____

Ima li bolesnik pridružena oboljenja?

❑ DA❑ NE❑Nije poznato

Ako je odgovor DA obeležite vrstu vrstu oboljenja:

Pridružena oboljenja:

- ❑ Hipertenzija
- ❑ Dislipidemija
- ❑ Drugo: _____

Dosadašnja antidijabetesna terapija

(Molimo označite sve što se odnosi na bolesnika)

❑Metformin **1** mg

❑Metformin **2** mg

❑Glimepirid **2** mg

❑Glimepirid **3** mg

❑Glimepirid **4** mg

Istovremena terapija drugim lekovima

❑Antihipertenzivi

_____(nezaštićeni naziv leka), u dozi _____

_____(nezaštićeni naziv leka),u dozi _____

❑ Statinska terapija

_____(nezaštićeni naziv leka), u dozi _____

❑Fibrati

_____(nezaštićeni naziv leka), u dozi _____

❑ Ostalo _____(upisati)

❑ Ostalo _____(upisati)

❑ Ostalo _____(upisati)

Oglition®
Oglition® početna doza **15** mg

„ Ja, dole potpisani/na, potvrđujem da sam pažljivo pregledao/la sve podatke unete u test listu ovog ispitanika. Prema mom saznanju, sve navedene informacije su tačne. „

Ime i prezime : _____

Potpis lekara: _____

Datum :|__|__| |__|__| |__|__|__|__|

Danmesec godina

V I Z I T A 2

(nakon 12 nedelja)

Datum posete: I__I__I I__I__I I__I__I__I__I Broj pacijenta: I__I__I

dan mesec godina

Glikemijski status

Glukoza našte I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I__I

dan mesec godina

HbA1c I__I__I, I__I % DatumI__I__I I__I__I I__I__I__I__I

dan mesec godina

Terapija

Da li je u ovoj poseti došlo do promene terapije Oglition®-om

❑ DA❑ NE

Ako je odgovor DA,upišite dozuOglition®-a koju ste preporučili :

❑Oglition®**30** mg

❑ Oglition®**45** mg

❑ Ukidanje leka Oglition®,objasnite_____

Da li je došlo do promene u terapiji metformina i/ili glimepirida

❑ DA❑ NE

Ako je odgovor DA, upišite dozu koju ste preporučili:

❑metformin, doza: _____

❑glimepirid ,doza: _____

Ukoliko je bolesnik na terapiji statinima/fibratima, da li je došlo do promene terapije:

❑ DA❑ NE

Ako je odgovor DA, upišite dozu koju ste preporučili:

❑statin _____(nezaštićeni naziv leka),doza _____

❑fibrat_____,(nezaštićeni naziv leka),doza _____

Neželjeni efekat / Ozbiljni neželjeni efekat
Je li bolesnik imao bilo kakav neželjeni događaj (AE) od poslednje vizite ? ❑ Da ❑ Ne Ako je odgovor pozitivan (DA),Ako je odgovor DA, molimo Vas da označite i prijavite Nacionalnom centru za farmakovigilancu ili SPONZORU : ☐glavobolja ☐hipoestezija ☐poremecaj vida ☐hematurija ☐erektilna disfunkcija ☐infekcija gornjeg respiratornog trakta ☐hipoglikemija ☐drugo _____ Je li bolesnik imao ozbiljnih neželjenih događaja (SAE) nakon poslednje vizite ? ❑ Da ❑ Ne *Obavestiti Sponzora u roku od 24 sata.*

„ Ja, dole potpisani/na, potvrđujem da sam pažljivo pregledao/la sve podatke unete u test listu ovog ispitanika. Prema mom saznanju, sve navedene informacije su tačne. ”

Ime i prezime : _____

Potpis lekara: _____

Datum :|__|__| |__|__| |__|__|__|__|

dan mesec godina

V I Z I T A 3

(nakon 24 nedelja)

Datum posete: I__I__I I__I__I I__I__I__I__I Broj pacijenta: I__I__I

dan mesec godina

Glikemijski status
Glukoza našte I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I__I *dan mesec godina* HbA1c I__I__I, I__I % Datum I__I__I I__I__I I__I__I__I__I *dan mesec godina*

Lipidni status
Upišite vrednosti i datum nalaza Ukupni holesterol I__I__I, I__I mmol/l Datum I__I__I I__I__I I__I__I__I__I *dan mesec godina* LDL Holesterol I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I__I *dan mesec godina* HDL Holesterol I__I__I, I__I mmol/L Datum I__I__I I__I__I I__I__I__I__I *dan mesec godina* Trigliceridi I__I__I, I__I mmol/L Datum I__I__I I__I__II__I__I__I__I *dan mesec godina*

Antropometrijski podaci

Telesna masa I__I__I__I (kg)

Obim struka I__I__I__I (cm)

Terapija

Da li je u ovoj poseti došlo do promene terapije Oglition®-om

❑ DA❑ NE

Ako je odgovor DA,upišite dozu Oglition®-a koju ste preporučili :

❑ Oglition®**30** mg

❑ Oglition®**45** mg

❑ Ukidanje leka Oglition®,objasnite_____

Da li je došlo do promene u terapiji metformina i/ili glimepirida u ovoj poseti

❑ DA❑ NE

Ako je odgovor DA, upišite dozu koju ste preporučili :

❑metformin doza: _____

❑glimepirid doza: _____

Ukoliko je bolesnik na terapiji statinima/fibratima, da li je došlo do promene terapije:

❑ DA❑ NE

Ako je odgovor DA, upišite dozu koju ste preporučili :

❑statin _____(nezaštićeni naziv leka),,doza _____

❑fibrat_____(nezaštićeni naziv leka),, doza _____

Neželjeni efekat / Ozbiljni neželjeni efekat

Je li bolesnik imao bilo kakav neželjeni događaj (AE)
od poslednje vizite ? ❑ Da ❑ Ne

Ako je odgovor pozitivan (DA),Ako je odgovor DA, molimo Vas da označite i prijavite Nacionalnom centru za farmakovigilancu ili SPONZORU :

☐glavobolja
☐hipoestezija
☐poremecaj vida
☐hematurija
☐erektilna disfunkcija
☐infekcija gornjeg respiratornog trakta
☐hipoglikemija
☐drugo _____

Je li bolesnik imao ozbiljnih neželjenih događaja (SAE)
nakon poslednje vizite ? ❑ Da ❑ Ne
Obavestiti Sponzora u roku od 24 sata.

Konačna procena lekara

Označite na skali od 1 ÷ 5 Vaš stav da li je lečenje Oglition®-om bilo efikasno (1 – najgori rezultat, 3 – neutralan, 5 – najbolji rezultat)

1	2	3	4	5

Označite na skali od 1 ÷ 5 Vaš stav da li je bolesnik dobro podnosio lečenje Oglition®-om (1 – najgori rezultat, 3 – neutralan, 5 – najbolji rezultat)

1	2	3	4	5

Da li nameravate da nastavite lečenje Oglition® -om ?❑Da❑ Ne

Ako je odgovor negativan (NE), objasnite :

_____

„ Ja, dole potpisani/na, potvrđujem da sam pažljivo pregledao/la sve podatke unete u test listu ovog ispitanika. Prema mom saznanju, sve navedene informacije su tačne. ”

Ime i prezime : _____

Potpis lekara: _____

Datum :|__|__| |__|__| |__|__|__|__|

Danmesec godina