



Clinical trial results:

A randomized controlled trial to evaluate the short-term efficacy and long-term health economic impact of a dietary intervention compared to pharmacotherapy with a musculotropic spasmolytic agent for newly diagnosed or newly treated irritable bowel syndrome in primary care.

Summary

EudraCT number	2017-003258-18
Trial protocol	BE
Global end of trial date	03 July 2020

Results information

Result version number	v1 (current)
This version publication date	14 March 2021
First version publication date	14 March 2021

Trial information

Trial identification

Sponsor protocol code	DOMINO
-----------------------	--------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04270487
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	UZLeuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Florencia Carbone, University Hospital Leuven, 0032 16345190, florencia.carbone@uzleuven.be
Scientific contact	Florencia Carbone, University Hospital Leuven, 0032 16345190, florencia.carbone@uzleuven.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 December 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	03 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary outcome is the improvement in IBS-Symptom Severity Score after 8 weeks of otilonium bromide compared to dietary intervention, with a 50-point drop being the established cut-off used in clinical trials. Based on our clinical experience and the available clinical data, we hypothesize that the dietary intervention will be superior to treatment with otilonium bromide 40 mg t.i.d. in improving IBS-SSS.

Protection of trial subjects:

study participants were followed up by their GP.

Study participants who had not yet finished the study during the Covid-19-pandemic were able to perform V3 and V4 by telephone.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 July 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 472
Worldwide total number of subjects	472
EEA total number of subjects	472

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	432
From 65 to 84 years	40

85 years and over	0
-------------------	---

Subject disposition

Recruitment

Recruitment details:

IBS patients were recruited by GPs in primary care

Pre-assignment

Screening details:

Patients were eligible if they were newly diagnosed with IBS or newly to be treated for IBS. The diagnostic gold standard, in line with clinical practice, was the clinician's diagnostic judgment. Also, patients who did not receive treatment with OB over the preceding 3 months, and who did not rece

Period 1

Period 1 title	overall study period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

patients were randomized to the diet or medication arm

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	lowering FODMAP diet
------------------	----------------------

Arm description:

The dietary arm in the study is the FODMAP lowering diet, also partially based on the dietary recommendations from the NICE and the British Dietetic Association. The diet was provided to the patients as a mobile phone application. The app included, among other tools, instructions to follow the diet, indications on what foods to avoid, to decrease ingestion or to use as alternatives. The possibility to acquire the diet on paper format was possible if the patient did not own a smart phone or tablet or if he had fail to download it.

Arm type	lowering FODMAP diet
----------	----------------------

No investigational medicinal product assigned in this arm

Arm title	Otilonium Bromide
------------------	-------------------

Arm description:

The medication arm in the study will use Otilonium Bromide (40 mg t.i.d.) which is a well-established and well-tolerated treatment modality. In accordance with the pragmatic design of this trial, patients received the medication prescribed by the GP and were requested to buy it at the pharmacy.

Arm type	Active comparator
Investigational medicinal product name	Otilonium Bromide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

The medication arm in the study will use Otilonium Bromide (40 mg t.i.d.). Patients randomized to the Otilonium Bromide arm, will take OB during 8 weeks (treatment phase). After the 8 week treatment phase they can continue the intake of OB during the follow up phase (16 weeks) or they can stop the intake of OB after the 8 week treatment phase and start another treatment during the FU phase (but they were not allowed to start a diet)

Number of subjects in period 1^[1]	lowering FODMAP diet	Otilonium Bromide
Started	227	232
end of treatment phase (8 weeks)	219	219
Completed	198	193
Not completed	29	39
Consent withdrawn by subject	17	20
Physician decision	-	2
concurrent disease	1	4
Lost to follow-up	2	2
Lack of efficacy	9	11

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Of the 472 included patients, 459 patients were randomized. 13 patients withdrew consent before randomization.

Baseline characteristics

Reporting groups

Reporting group title	overall study period
-----------------------	----------------------

Reporting group description:

459 patients were randomized

Reporting group values	overall study period	Total	
Number of subjects	459	459	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	423	423	
From 65-84 years	36	36	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	40.9		
standard deviation	± 14.7	-	
Gender categorical			
Units: Subjects			
Female	343	343	
Male	116	116	

End points

End points reporting groups

Reporting group title	lowering FODMAP diet
Reporting group description: The dietary arm in the study is the FODMAP lowering diet, also partially based on the dietary recommendations from the NICE and the British Dietetic Association. The diet was provided to the patients as a mobile phone application. The app included, among other tools, instructions to follow the diet, indications on what foods to avoid, to decrease ingestion or to use as alternatives. The possibility to acquire the diet on paper format was possible if the patient did not own a smart phone or tablet or if he had fail to download it.	
Reporting group title	Otilonium Bromide
Reporting group description: The medication arm in the study will use Otilonium Bromide (40 mg t.i.d.) which is a well-established and well-tolerated treatment modality. In accordance with the pragmatic design of this trial, patients received the medication prescribed by the GP and were requested to buy it at the pharmacy.	

Primary: treatment responder rate after 8 weeks

End point title	treatment responder rate after 8 weeks
End point description: IBS – symptom severity score scale (IBS-SSS) questionnaire: To assess the severity of IBS. The maximum achievable score is 500. Mild, moderate and severe cases were indicated by scores of 75 to 175, 175 to 300 and >300 respectively. Controls scored below 75 and patients scoring in this range can be considered to be in remission.	
End point type	Primary
End point timeframe: The primary outcome variable of the trial was treatment responder rate after 8 weeks. A responsive patient was defined as a patient with at least 50-point drop from baseline on the IBS IBS-SSS.	

End point values	lowering FODMAP diet	Otilonium Bromide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	231		
Units: %				
number (not applicable)	71.1	61.3		

Statistical analyses

Statistical analysis title	Responder rate (low FODMAP diet vs OB)
Statistical analysis description: The primary outcome variable of the trial was treatment responder rate after 8 weeks. A responsive patient was defined as a patient with at least 50-point drop from baseline on the IBS-SSS.	
Comparison groups	lowering FODMAP diet v Otilonium Bromide

Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.03
Method	Mixed models analysis

Notes:

[1] - All analyses were conducted on an intention-to-treat (ITT) basis. For this analysis, the responder status was determined for all patients and the proportion of responders was compared between treatment arms using mixed effect logistic regression (MELR) which is effectively a mixed-model logistic regression in which treatment group is treated as a fixed effect and general practice as a random effect.

Secondary: Change in IBS-SSS (end - start)

End point title	Change in IBS-SSS (end - start)
-----------------	---------------------------------

End point description:

Treatment efficacy calculated using the change in IBS-symptom severity score scale (IBS-SSS). The IBS-SSS is used to assess the severity of IBS. The maximum achievable score is 500. Mild, moderate and severe cases were indicated by scores of 75 to 175, 175 to 300 and >300 respectively. Controls scored below 75 and patients scoring in this range can be considered to be in remission.

End point type	Secondary
----------------	-----------

End point timeframe:

Treatment efficacy after 8 weeks of treatment (low FODMAP diet vs Otilonium Bromide)
The change score for IBS-SSS was calculated as change from baseline to end of treatment phase.

End point values	lowering FODMAP diet	Otilonium Bromide		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	222	231		
Units: score				
arithmetic mean (standard deviation)	-97.9 (± 8.6)	-77.4 (± 8.4)		

Statistical analyses

Statistical analysis title	Change in IBS symptom severity score
----------------------------	--------------------------------------

Statistical analysis description:

The change score for IBS-SSS and all specified quantitative outcomes was calculated as change from baseline to end of therapy. Comparison of treatment groups employed linear regression with change score as the outcome variable and a single dummy-coded independent variable representing treatment group membership as the independent variable.

Comparison groups	lowering FODMAP diet v Otilonium Bromide
Number of subjects included in analysis	453
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Linear

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

from signing the informed consent form until 30 days after the final study visit

Adverse event reporting additional description:

The DOMINO trial was considered a low risk trial. Information regarding adverse events (AE) and serious adverse events (SAE) for the study treatments was indicated to GPs but collection of these data specific for this trial was not requested. Only serious adverse reactions (SAR) clearly related to OB were to be registered in the eCRF by the GP.

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	20
--------------------	----

Frequency threshold for reporting non-serious adverse events: 1 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: The DOMINO trial was considered a low risk trial. For this reason, information regarding adverse events (AE) for the study treatments was indicated to GPs but collection of these data specific for this trial was not requested. It was the GP's responsibility to determine all AEs and SAEs and manage them in the patient's medical record in accordance with standard clinical practice guidelines, and this for up to 30 days after the end of the trial.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 June 2018	protocol versie 6 (04/04/2018); ICF versie 3 (04/04/2018) (NI + Fr); eCRF: automatische e-mailnotificaties naar patiënten (NI + Fr); Toevoeging van de lijst met 80 huisartsen-onderzoekers **
17 July 2018	protocol versie 7 (11/06/2018); ICF versie 4 (11/06/2018) (NI + Fr)
18 October 2018	Toevoeging van de lijst met 21 huisartsen-onderzoekers
05 March 2019	Toevoeging van 6 bijkomende huisartsen-onderzoekers ** Toevoeging van GDPR informatieformulier voor patiënten (NI + Fr)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported