Supplementary material

The trial website was set up at www.TOPPITS.co.uk

List of Supplementary Tables

List of Supplementary Figures

Table 1: Confirmation of balanced numbers of participants in each treatment group by stratification factor site for ITT population

Site	**Lansoprazole N=172**	**Placebo N=174**	**Total N=346**
Newcastle	66 (38%)	67 (39%)	133 (38%)
Nottingham	34 (20%)	36 (21%)	70 (20%)
Sunderland	24 (14%)	23 (13%)	47 (14%)
Glasgow	18 (10%)	21 (12%)	39 (11%)
Manchester	15 (9%)	12 (7%)	27 (8%)
Stockport	5 (3%)	6 (3%)	11 (3%)
Birmingham	5 (3%)	5 (3%)	10 (3%)
Brighton	5 (3%)	4 (2%)	9 (3%)
All sites	**172 (100%)**	**174 (100%)**	**346 (100%)**

Table 2: Participants mis-stratified based on baseline severity using RSI-HB

Stratification: mild 10<=RSI-HB<=20; severe RSI-HB>20

Study ID	**Arm**	**Baseline severity assigned**	**Baseline RSI-HB score**
1042	Lansoprazole	Mild	23
1011	Lansoprazole	Mild	21
5013	Lansoprazole	Mild	24
6009	Lansoprazole	Mild	21
5003	Lansoprazole	Mild	23
5011	Lansoprazole	Mild	30
2007	Lansoprazole	Mild	21
2123	Lansoprazole	Severe	20
2109	Lansoprazole	Severe	18
2126	Lansoprazole	Severe	15
4106	Lansoprazole	Severe	10
4103	Lansoprazole	Severe	18
1116	Lansoprazole	Severe	17
3103	Lansoprazole	Severe	19
2121	Lansoprazole	Severe	14
4102	Lansoprazole	Severe	19
1102	Lansoprazole	Severe	15
3127	Lansoprazole	Severe	17
2130	Lansoprazole	Severe	18
2112	Lansoprazole	Severe	20
1136	Lansoprazole	Severe	20
5101	Lansoprazole	Severe	10
3133	Lansoprazole	Severe	16
6011	Placebo	Mild	25
1014	Placebo	Mild	21
5014	Placebo	Mild	21
5010	Placebo	Mild	34
5019	Placebo	Mild	21
3128	Placebo	Severe	13
4104	Placebo	Severe	18
4101	Placebo	Severe	20
1117	Placebo	Severe	15
3126	Placebo	Severe	17
7107	Placebo	Severe	19
1124	Placebo	Severe	20
1140	Placebo	Severe	17

Table 3: Participants with missing baseline RSI-HB

Study ID	Arm	Date randomised	Date of withdrawal	Reason for withdrawal
2106	PPI	12/11/14	12/11/14	Consented in error - ineligible
4002	Placebo	03/06/15	22/07/15	Baseline data collected but missing one RSI item
1062	Placebo	04/05/16	N/A	Randomised in error pre-wash out; thereafter ineligible
5022	Placebo	12/10/16	29/05/17	Baseline data collected but missing one RSI item

Table 4: 17 participants who withdrew before primary endpoint visit

Study ID	Arm	Date randomised	Primary endpoint Visit 2	Primary outcome (RSI Visit 2)	Date of withdrawal	Reason for withdrawal
1072	PPI	14/09/2016	04/01/2017		29/09/2016	Stopped IMP; declined rest of trial.
1121	PPI	22/09/2015	08/03/2016	1	10/11/2015	Back rash 4/10/15
1126	PPI	20/10/2015	09/02/2016	31	10/11/2015	Rash on torso and head 31/10/2015. PI advised discontinue -after antihistamines from GP
1144	PPI	14/09/2016	04/01/2017		01/11/2016	Lost to follow-up.
1146	PPI	28/11/2016	12/04/2017		28/11/2016	Lost to follow-up.
3127	PPI	27/11/2015	11/03/2016	17	23/02/2016	Stopped IMP (no benefit); GP started Omeprazole
6009	PPI	08/04/2016	13/06/2016	17	30/05/2016	Weakness in left limb, chest pain, confusion.
1004	Placebo	22/07/2014	03/11/2014	27	02/09/2014	Headaches
1071	Placebo	05/09/2016	19/07/2017		01/11/2016	Withdrew
1080	Placebo	28/11/2016	12/04/2017		01/01/2017	Lost to follow-up
3013	Placebo	29/05/2015	21/08/2015	17	29/05/2015	Side effects to IMP- at 4 weeks'
3107	Placebo	07/11/2014	27/02/2015	29	12/01/2015	IMP interrupted due to AEs x2; then withdrew
3110	Placebo	19/12/2014	17/04/2015	15	20/03/2015	Symptoms worse - participant suspected gluten intolerance to placebo.
3112	Placebo	09/01/2015	01/05/2015	26	05/03/2015	Severe pressure headache from 29/01/2015
5022	Placebo	12/10/2016	15/06/2017		29/05/2017	Telephoned to withdraw; handed IMP to local pharmacy; then lost to follow-up.
4002	Placebo	03/06/2015	22/07/2015		22/07/2015	Not stated
5010	Placebo	20/01/2016	10/02/2016	20	10/02/2016	Ineligible

Table 5: 14 participants who withdrew at primary endpoint visit

Study ID	Arm	Date Randomised	Primary endpoint visit	Primary outcome (RSI Visit 2)	Date of withdrawal	Reason for withdrawal
1081	PPI	21/12/2016	03/05/2017	6	03/05/2017	Lost to follow-up
1113	PPI	09/06/2015	19/01/2016	25	19/01/2016	Did not attend Visit 3
1130	PPI	19/01/2016	04/05/2016	13	04/05/2016	Lost to follow-up
3029	PPI	12/08/2016	02/12/2016		02/12/2016	New medical diagnosis given -off-study PPI
5001	PPI	19/08/2015	07/10/2015		07/10/2015	Gastrointestinal side-effects.
7105	PPI	14/10/2016	22/02/2017	25	22/02/2017	Noncompliant with IMP from the start
1021	Placebo	04/02/2015	01/06/2015	26	01/06/2015	Did not attend Visit 3
1069	Placebo	10/08/2016	01/02/2017	8	01/02/2017	Not stated
1070	Placebo	10/08/2016	12/04/2017	15	12/04/2017	Lost to follow-up
1079	Placebo	16/11/2016	12/04/2017	30	12/04/2017	Lost to follow-up
1084	Placebo	04/01/2017	17/05/2017	5	17/05/2017	Lost to follow-up
1111	Placebo	13/01/2015	28/07/2015	32	28/07/2015	Did not attend Visit 3
1131	Placebo	09/02/2016	28/06/2016	25	28/06/2016	Lost to follow-up
3016	Placebo	25/09/2015	08/01/2016	13	08/01/2016	Noncompliant with IMP from start

Per treatment group Safety data –

Table 6: Line listing of AEs categorised as **probably related to treatment** by severity of AEs on per treatment population while taking the trial medication (**between randomisation and primary endpoint**)

Study ID	Arm	Date randomised	Primary endpoint visit date	Adverse Event details	Start date	Stop date	Severity
1074	Lansoprazole	28/09/2016	01/02/2017	Rash	01/10/2016	20/11/2016	Severe
1101	Lansoprazole	09/06/2014	13/10/2014	Abdominal discomfort	08/07/2014		Moderate
1106	Lansoprazole	17/11/2014	30/03/2015	Stomach Pains	17/11/2014	30/03/2015	Moderate
1016	Lansoprazole	01/12/2014	18/03/2015	Nausea / Vomiting, Stopped Drug in February 2015 and nausea settled. Still able to eat.	01/12/2014		Moderate
2002	Lansoprazole	17/07/2014	12/11/2014	Rash	31/07/2014	07/08/2014	Moderate
5001	Lansoprazole	19/08/2015	07/10/2015	Participant experienced adverse gastrointestinal symptoms	22/08/2015	31/08/2015	Moderate

Table 7: Line listing of AEs categorised as **possibly related to treatment** by severity of AEs on per treatment population while taking the trial medication (**between randomisation and primary endpoint**)

Study ID	Arm	Date randomised	Primary endpoint visit date	Adverse Event details	Start date	Stop date	Severity
1126	Lansoprazole	20/10/2015	09/02/2016	rash on torso and head	31/10/2015	02/11/2015	Moderate
1121	Lansoprazole	22/09/2015	08/03/2016	Rash on spine	04/10/2015	19/10/2015	Moderate
3023	Lansoprazole	05/02/2016	03/06/2016	Severe Headaches	12/02/2016		Moderate
1028	Lansoprazole	21/04/2015	20/07/2015	Stomach Cramps and Diarrhoea	10/05/2015	22/05/2015	Moderate
5108	Lansoprazole	04/05/2016	14/09/2016	Diarrhoea as a result of IMP	04/05/2016	07/06/2016	Moderate
8003	Lansoprazole	11/08/2016	01/12/2016	Diarrhoea	01/11/2016	08/11/2016	Mild
3105	Lansoprazole	31/10/2014	20/02/2015	Loose bowels	02/11/2014		Mild
3018	Lansoprazole	06/11/2015	26/02/2016	Nausea intermittent	14/11/2015		Mild
3012	Lansoprazole	01/05/2015	21/08/2015	Stomach Discomfort	02/05/2015	06/06/2015	Mild
3012	Lansoprazole	01/05/2015	21/08/2015	Constipation	02/05/2015	06/06/2015	Mild
1048	Lansoprazole	13/10/2015	15/03/2016	Constipation	11/03/2016		Mild
8003	Lansoprazole	11/08/2016	01/12/2016	loose bowels	12/08/2016		Mild
1119	Placebo	04/08/2015	22/12/2015	Bloating lump in throat dyspepsia	01/10/2015		Moderate

3110	Placebo	19/12/2014	17/04/2015	Study Drug appears to make symptoms worse	17/01/2015	07/02/2015	Moderate
3112	Placebo	09/01/2015	01/05/2015	Severe pressure-like headaches	29/01/2015		Moderate
8101	Placebo	22/03/2016	11/07/2016	Flatulence	23/03/2016		Mild
1138	Placebo	18/05/2016	28/09/2016	Diarrhoea	15/06/2016	28/09/2016	Mild
1004	Placebo	22/07/2014	03/11/2014	headaches and stomach pains	22/07/2014	30/07/2014	Mild

Table 8: Line listing of AEs categorised as **not related to treatment** by severity of AEs on per treatment population while taking the trial medication (**between randomisation and primary endpoint**) – lansoprazole

Study ID	Arm	Date randomised	Primary endpoint visit date	Adverse Event details	Start date	Stop date	Severity
3029	Lansoprazole	12/08/2016	02/12/2016	Polyarthritis	01/09/2016		Severe
3132	Lansoprazole	29/04/2016	19/08/2016	Nausea, Vomiting	23/06/2016	16/07/2016	Moderate
3130	Lansoprazole	26/02/2016	24/06/2016	Headaches	01/04/2016	04/04/2016	Moderate
3132	Lansoprazole	29/04/2016	19/08/2016	Stomach cramps	23/06/2016	16/07/2016	Moderate
3139	Lansoprazole	22/02/2017	09/06/2017	Left upper quadrant abdominal pain	23/03/2017		Moderate
7106	Lansoprazole	27/10/2016	23/02/2017	Back pain	28/12/2016		Moderate
7106	Lansoprazole	27/10/2016	23/02/2017	Vomiting	28/12/2016	20/02/2017	Moderate
7106	Lansoprazole	27/10/2016	23/02/2017	Cough	28/12/2016		Moderate
7105	Lansoprazole	14/10/2016	22/02/2017	Burning sensation in throat	14/10/2016		Moderate
3132	Lansoprazole	29/04/2016	19/08/2016	Severe Headaches	01/05/2016	15/05/2016	Moderate
7106	Lansoprazole	27/10/2016	23/02/2017	Acid Reflux	21/02/2017		Moderate
3132	Lansoprazole	29/04/2016	19/08/2016	Gallbladder	01/08/2016		Moderate
3113	Lansoprazole	16/01/2015	08/05/2015	Self diagnosed chest infection	07/02/2015	21/02/2015	Mild
3122	Lansoprazole	07/08/2015	20/11/2015	Peripheral vision disturbance	20/08/2015	20/08/2015	Mild
3031	Lansoprazole	20/01/2017	09/06/2017	Central abdominal pain	15/03/2017	16/03/2017	Mild
3027	Lansoprazole	22/07/2016	11/11/2016	Common cold	08/11/2016	09/11/2016	Mild
3019	Lansoprazole	15/12/2015	08/04/2016	Self-diagnosed food poisoning	22/12/2015	24/12/2015	Mild
6105	Lansoprazole	08/04/2016	08/08/2016	colonoscopy	14/06/2016	14/06/2016	Mild
3014	Lansoprazole	14/08/2015	18/12/2015	Low mood	01/10/2015		Mild
3123	Lansoprazole	04/09/2015	18/12/2015	Head cold with coughing	01/12/2015	16/12/2015	Mild
3022	Lansoprazole	29/01/2016	27/05/2016	Sore throat due to common cold	13/05/2016		Mild

3011	Lansoprazole	20/03/2015	07/08/2015	Viral infection Throat	14/07/2015	03/08/2015	Mild
6110	Lansoprazole	23/09/2016	27/01/2017	chest infection	30/12/2016	06/01/2017	Mild
4003	Lansoprazole	04/11/2015	24/02/2016	wind / diarrhoea	18/11/2015	22/11/2015	Mild

Table 9: Line listing of AEs categorised as **not related to treatment** by severity of AEs on per treatment population while taking the trial medication (**between randomisation and primary endpoint**). Participants randomised to placebo

Study ID	Arm	Date randomised	Primary endpoint visit date	Adverse Event details	Start date	Stop date	Severity
1033	Placebo	13/05/2015	07/09/2015	Participant had colic x3, lasting 1 hour	07/08/2015		Severe
8004	Placebo	11/10/2016	07/02/2017	Participant developed high altitude pulmonary oedema during holiday in America	02/01/2017	04/01/2017	Severe
3013	Placebo	29/05/2015	21/08/2015	voice fatigue	19/06/2015	10/07/2015	Moderate
3013	Placebo	29/05/2015	21/08/2015	Difficulty swallowing	19/06/2015	10/07/2015	Moderate
3002	Placebo	12/09/2014	09/01/2015	Elective surgery	22/10/2014	22/10/2014	Moderate
3102	Placebo	10/10/2014	30/01/2015	Viral Infection	20/12/2014	05/01/2015	Moderate
3013	Placebo	29/05/2015	21/08/2015	Pain/Constriction at back of throat	19/06/2015	10/07/2015	Moderate
3107	Placebo	07/11/2014	27/02/2015	Transient Global Amnesia	27/11/2014	27/11/2014	Moderate
3009	Placebo	02/01/2015	01/05/2015	chest Infection	30/03/2015	14/04/2015	Moderate
3009	Placebo	02/01/2015	01/05/2015	Chest infection	18/11/2014	30/11/2014	Moderate
1143	Placebo	17/08/2016	23/08/2017	Left eye evisceration for recurrent eye ulceration	27/02/2017	09/03/2017	Moderate
1143	Placebo	17/08/2016	23/08/2017	Insertion of septal button to septal perforation	06/04/2017	07/04/2017	Moderate
3135	Placebo	21/10/2016	01/03/2017	Common Cold	14/12/2016	23/12/2016	Mild
8005	Placebo	03/11/2016	18/05/2017	Electric shock from a fridge	30/04/2017		Mild
3135	Placebo	21/10/2016	01/03/2017	Common Cold	23/02/2017		Mild
5110	Placebo	27/07/2016	07/12/2016	Pins and needles	01/12/2016	01/03/2017	Mild
3136	Placebo	02/12/2016	07/04/2017	Acid Reflux	28/12/2016		Mild
3124	Placebo	25/09/2015	22/01/2016	Intermittent chest pain	03/10/2015	30/11/2015	Mild
8006	Placebo	19/01/2017	18/05/2017	Intermittent headaches	19/02/2017		Mild

5005	Placebo	23/12/2015	20/04/2016	chest infection	28/03/2016	04/04/2016	Mild
3003	Placebo	26/09/2014	16/01/2015	Flu Symptoms	13/11/2014	25/11/2014	Mild
3124	Placebo	25/09/2015	22/01/2016	Intermittent numbness of left arm	03/10/2015	30/11/2015	Mild
3120	Placebo	10/07/2015	30/10/2015	Recurrent ear infections bilateral	01/10/2015		Mild
3001	Placebo	08/08/2014	28/11/2014	Throat virus	27/09/2014	30/09/2014	Mild
3003	Placebo	26/09/2014	16/01/2015	Flu symptoms	10/01/2015		Mild
5024	Placebo	21/12/2016	12/04/2017	Dry mouth	01/01/2017		Mild
3010	Placebo	06/03/2015	26/06/2015	Poss. food poisoning, sickness and vomiting	13/04/2015	15/04/2015	Mild
5010	Placebo	20/01/2016	10/02/2016	Ineligible	20/01/2016		Mild
3107	Placebo	07/11/2014	27/02/2015	Sores, bleeding burning sensation in nose	20/12/2014		Mild
3102	Placebo	10/10/2014	30/01/2015	bad cold	12/11/2014	16/11/2014	Mild
3134	Placebo	21/10/2016	17/02/2017	Flu	06/02/2017	10/02/2017	Mild
3026	Placebo	24/06/2016	20/10/2016	pain in hips, knees, ankle	26/06/2016		Mild

Table 10: Line listing of AEs categorised as **not related to treatment** by severity of AEs on per treatment population while NOT taking the trial medication (**after primary endpoint**)

Study ID	Arm	Date randomised	Primary endpoint visit date	Adverse Event details	Start date	Stop date	Severity
1034	Lansoprazole	13/05/2015	22/09/2015	upper right quadrant pain	15/10/2015	08/04/2016	Moderate
7002	Lansoprazole	19/07/2016	15/11/2016	Chest infection	22/06/2017	20/07/2017	Moderate
3023	Lansoprazole	05/02/2016	03/06/2016	Migraine	09/01/2017	11/01/2017	Moderate
3019	Lansoprazole	15/12/2015	08/04/2016	Recurrence of Lymphoma	12/05/2016		Moderate
3132	Lansoprazole	29/04/2016	19/08/2016	Flu	20/10/2016	03/11/2016	Mild
3130	Lansoprazole	26/02/2016	24/06/2016	Headache	26/12/2016	31/12/2016	Mild
3130	Lansoprazole	26/02/2016	24/06/2016	Headache	06/02/2017		Mild
3017	Lansoprazole	06/11/2015	19/02/2016	Cough	04/11/2016		Mild
4106	Lansoprazole	07/10/2015	27/01/2016	Vomiting	18/08/2016	19/08/2016	Mild
3024	Lansoprazole	26/02/2016	24/06/2016	Allergy - puffy eyes	17/02/2017	24/02/2017	Mild
4106	Lansoprazole	07/10/2015	27/01/2016	Diarrhoea	18/08/2016	19/08/2016	Mild
8003	Lansoprazole	11/08/2016	01/12/2016	Persistent cough	20/08/2017		Mild
3022	Lansoprazole	29/01/2016	27/05/2016	Upper airway tract infection	19/12/2016		Mild
3130	Lansoprazole	26/02/2016	24/06/2016	Common cold	26/12/2016	31/12/2016	Mild
3027	Lansoprazole	22/07/2016	11/11/2016	Intermittent Acid Reflux	01/12/2016		MISSING
3112	Placebo	09/01/2015	01/05/2015	Helicobacter infection	22/11/2015	04/01/2016	Moderate
3107	Placebo	07/11/2014	27/02/2015	Transient Global Amnesia	30/07/2015	30/07/2015	Moderate
3020	Placebo	22/12/2015	08/04/2016	Tonsillitis	18/11/2016	16/12/2016	Mild
3128	Placebo	22/01/2016	20/05/2016	A Cold	12/12/2016	18/12/2016	Mild
3020	Placebo	22/12/2015	08/04/2016	Dry tickly cough	18/11/2016		Mild
3128	Placebo	22/01/2016	20/05/2016	Indigestion	23/12/2016		Mild

5110	Placebo	27/07/2016	07/12/2016	Depression	18/08/2017		Mild
3025	Placebo	11/03/2016	24/06/2016	Vertigo Attack	25/03/2017	25/03/2017	Mild
3128	Placebo	22/01/2016	20/05/2016	Intermittent mouth ulcers	09/01/2017	15/01/2017	Mild
3131	Placebo	08/04/2016	29/07/2016	Nasal Polyps	20/10/2016		Mild
3021	Placebo	29/01/2016	20/05/2016	Sickness bug	12/09/2016	13/09/2016	Mild
3131	Placebo	08/04/2016	29/07/2016	Allergy	28/10/2016		Mild
3021	Placebo	29/01/2016	20/05/2016	Cramping stomach	16/02/2017	17/02/2017	Mild
3008	Placebo	12/12/2014	17/04/2015	Gum Infection	09/12/2015		Mild

*3027 has ‘related to treatment’ category missing as well as severity

Table 11: Line listing of AEs categorised as **not related to treatment** by severity of AEs on per treatment population not categorised as during or after treatment (missing AE dates)

Study ID	Arm	Date randomised	Primary endpoint visit date	Adverse Event details	Start date	Stop date	Severity
3022	Lansoprazole	29/01/2016	27/05/2016	Vomiting			Moderate
3023	Lansoprazole	05/02/2016	03/06/2016	Acid Reflux			Mild
3024	Lansoprazole	26/02/2016	24/06/2016	Arthritis			Mild

*update from data manager – exact dates not known. The two mild AEs (3023 & 3024) pre-date the trial so shouldn't be included at all. The AE in 3022 is marked as not available at site in MACRO

Table 12: Itemised scores for CReSS for whole trial population (Item Range 0-5) n=335

CReSS Item	Mean	SD	Median	IQR
1 – Heartburn	1.4	1.5	1	(0, 2)
2 – Pressure in chest	1.1	1.4	0	(0, 2)
3 – Regurgitation	1.1	1.4	1	(0, 2)
4 – Acid/sour taste in mouth	1.5	1.5	1	(0, 3)
5 – Gurgling stomach	1.7	1.6	1	(0, 3)
6 – Lump in throat	2.9	1.7	3	(1, 4)
7 – Difficulty swallowing food	1.4	1.6	1	(0, 3)
8 – Difficulty swallowing liquids	0.8	1.2	0	(0, 1)
9 – Nausea	0.9	1.4	0	(0, 2)
10 – Pain in throat	1.5	1.6	1	(0, 3)
11 – Vomiting	0.4	1.0	0	(0, 0)
12 – Bloating	1.4	1.6	1	(0, 2)
13 – Belching	1.4	1.6	1	(0, 3)
14 – Flatulence	1.5	1.6	1	(0, 3)
15 – Hiccups	0.6	1.1	0	(0, 1)
16 – Decreased appetite	0.7	1.3	0	(0, 1)
17 – Rush of saliva in mouth	1.2	1.5	1	(0, 2)
18 – Feeling full early	1.1	1.5	0	(0, 2)
19 – Bad breath	1.1	1.4	0	(0, 2)
20 – Back pain	1.9	1.7	2	(0, 3)
21 – Headache	1.4	1.8	1	(0, 2)
22 – Choking	1.1	1.5	0	(0, 2)
23 – Coughing upright	2.0	1.6	2	(0, 3)
24 – Coughing after eating	1.5	1.6	1	(0, 3)
25 – Coughing lying down	2.0	1.7	2	(0, 3)
26 – Wheezing	1.1	1.5	0	(0, 2)
27 – Difficulty breathing	1.1	1.6	0	(0, 2)
28 – Hoarseness	2.1	1.8	2	(0, 4)
29 – Throat clearing	3.2	1.5	4	(2, 4)
30 – Excess mucous	2.4	1.8	2	(1, 4)
31 – Mucous dripping in throat	2.1	1.9	2	(0, 4)
32 – Feeling things stuck in throat	2.9	1.8	3	(1, 4)
33 – Indigestion	1.3	1.5	1	(0, 2)
34 – Stomach acid coming up	1.4	1.6	1	(0, 3)

Table 13: Itemised scores for CReSS (Item Range 0-5), compliant group n=220

CReSS Item	n	Mean	SD	Median	IQR
1 – Heartburn	218	1.3	1.4	1	(0, 2)
2 – Pressure in chest	218	1.1	1.4	0	(0, 2)
3 – Regurgitation	218	1.1	1.3	1	(0, 2)
4 – Acid/sour taste in mouth	218	1.6	1.5	1	(0, 3)
5 – Gurgling stomach	218	1.7	1.5	1	(0, 3)
6 – Lump in throat	218	2.9	1.8	3	(1 ,4)
7 – Difficulty swallowing food	218	1.4	1.6	1	(0, 2)
8 – Difficulty swallowing liquids	218	0.8	1.2	0	(0, 1)
9 – Nausea	218	0.9	1.3	0	(0, 1)
10 – Pain in throat	218	1.5	1.6	1	(0, 3)
11 – Vomiting	218	0.4	1.0	0	(0, 0)
12 – Bloating	218	1.3	1.6	1	(0, 2)
13 – Belching	218	1.4	1.5	1	(0, 2)
14 – Flatulence	218	1.6	1.6	1	(0, 3)
15 – Hiccups	218	0.6	1.0	0	(0, 1)
16 – Decreased appetite	218	0.7	1.2	0	(0, 1)
17 – Rush of saliva in mouth	218	1.1	1.4	0	(0, 2)
18 – Feeling full early	216	1.1	1.5	0	(0, 2)
19 – Bad breath	217	0.9	1.3	0	(0, 2)
20 – Back pain	218	1.9	1.7	2	(0, 3)
21 – Headache	218	1.3	1.4	1	(0, 2)
22 – Choking	218	1.1	1.5	0	(0, 2)
23 – Coughing upright	218	2.0	1.6	2	(1, 3)
24 – Coughing after eating	218	1.6	1.6	1	(0, 3)
25 – Coughing lying down	218	2.0	1.8	2	(0, 4)
26 – Wheezing	218	1.1	1.5	0	(0, 2)
27 – Difficulty breathing	218	1.1	1.6	0	(0, 2)
28 – Hoarseness	218	2.1	1.8	2	(0, 4)
29 – Throat clearing	217	3.2	1.5	4	(2, 4)
30 – Excess mucous	218	2.4	1.8	2	(1, 4)
31 – Mucous dripping in throat	218	2.0	1.9	2	(0, 4)
32 – Feeling things stuck in throat	218	2.9	1.8	3	(1, 5)
33 – Indigestion	218	1.3	1.4	1	(0, 2)
34 – Stomach acid coming up	218	1.5	1.5	1	(0, 3)

Table 14: Compliance primary outcome measure – Number of RSI items at baseline and 16 week follow up with follow up completed at various times after randomisation

Visit	RSI completeness	Lansoprazole (N=172)	Placebo (N=174)	Total (N=346)
Baseline visit 1	Returns with 9 items	171 (99%)	171 (98%)	342 (99%)
	Incomplete (1-8 items)	0 (0%)	2 (1%)	2 (>1%)
	Completely missing (0 items)	1 (>1%)	1 (>1%)	2 (>1%)
16 week visit 2 (Protocol group 16 week +/- 2 week – 14 to 18 weeks post randomisation)	Returns with 9 items	82 (48%)	96 (55%)	178 (51%)
	Incomplete (1-8 items)	0 (0%)	0 (0%)	0 (0%)
	Completely missing (0 items)	5 (3%)	2 (1%)	7 (2%)
16 week visit 2 (Compliant ITT - 14 to 20 weeks post randomisation)	Returns with 9 items	102 (59%)	118 (68%)	220 (64%)
	Incomplete (1-8 items)	0 (0%)	0 (0%)	0 (0%)
	Completely missing (0 items)	6 (3%)	3 (2%)	9 (3%)
16 week visit 2 (Pragmatic ITT group at any time)	Returns with 9 items	127 (74%)	140 (80%)	267 (77%)
	Incomplete (1-8 items)	0 (0%)	0 (0%)	0 (0%)
	Completely missing (0 items	8 (5%)	8 (5%)	16 (5%)
No 16 week visit 2	**No RSI (as no visit 2)**	**37 (22%)**	**26 (15%)**	**63 (18%)**

Compliance to RSI questionnaire items at baseline and primary end point visit is reported in table 14. The table shows the number of RSI questionnaires returned at baseline (shaded green) and the primary endpoint visits for the protocol group (shaded grey), compliant ITT group (shaded blue), and the pragmatic ITT group (shaded grey) with all 9 items completed as well as numbers with less than 9 items completed and number totally missing. The final row in the table (shaded grey) details how many participants did not attend their primary endpoint visit and so had no follow up RSI questionnaire (withdrawn or lost to follow up).

Table 15: RSI within/outside normal range at baseline and follow up visits, compliant ITT (n=220)

RSI normal range	**Baseline**			**16 week**			**12 month**		
	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total	Lansoprazole	Placebo	Total
N (%)	102 (100%)	118 (100%)	220 (100%)	102 (100%)	118 (100%)	220 (100%)	82 (80%)	99 (84%)	181 (82%)
Within (RSI: 0-12)	11 (11%)	12 (10%)	23 (10%)	42 (41%)	53 (45%)	95 (43%)	33 (40%)	54 (55%)	87 (48%)
Outside (RSI>12)	91 (89%)	106 (90%)	197 (90%)	60 (59%)	65 (55%)	125 (57%)	49 (60%)	45 (45%)	94 (52%)

Table 16 Itemised scores for RSI (Item Range 0-5) for trial population (n=342)

RSI item	Mean	SD	Median	IQR
1 – Hoarseness	2.4	1.6	3	(1, 4)
2 – Throat clearing	3.4	1.3	4	(3, 4)
3 – Excess throat mucus	2.9	1.6	3	(2, 4)
4 – Difficulty swallowing	1.7	1.6	2	(0, 3)
5 – Coughing after eating or lying down	2.1	1.6	2	(0, 3)
6 – Breathing difficulties	1.6	1.6	1	(0, 3)
7 – Troublesome cough	2.5	1.7	3	(1, 4)
8 – Lump in throat	3.5	1.4	4	(3, 5)
9 - Heartburn	1.8	1.6	1.5	(0, 3)

Table 17 Itemised score for RSI at baseline for compliant ITT group (n=220)

RSI item	Mean	SD	Median	IQR
1 – Hoarseness	2.4	1.6	3	(1, 4)
2 – Throat clearing	3.4	1.3	4	(3, 4)
3 – Excess throat mucus	2.9	1.5	3	(2, 4)
4 – Difficulty swallowing	1.6	1.6	1	(0, 3)
5 – Coughing after eating or lying down	2.2	1.7	2	(1, 3.5)
6 – Breathing difficulties	1.6	1.6	1	(0, 3)

7 – Troublesome cough	2.5	1.7	3	(1, 4)
8 – Lump in throat	3.5	1.5	4	(3, 5)
9 - Heartburn	1.9	1.6	2	(0, 3)

Plots of laryngopharyngeal reflux health related quality of life (Subscales and corresponding Thermometer scores)

The charts presented in this section (figures 1 to 8) show the aggregated LPR HRQL subscale scores relating to a particular aspect of quality of life and corresponding aggregated Thermometer scores. The subscale scores are presented as mean values with 95% confidence intervals and thermometer scores as median and interquartile range, scale range: 1 to 10. Each chart shows aggregated scores at baseline, 16 weeks and 12 months separately for each treatment arm

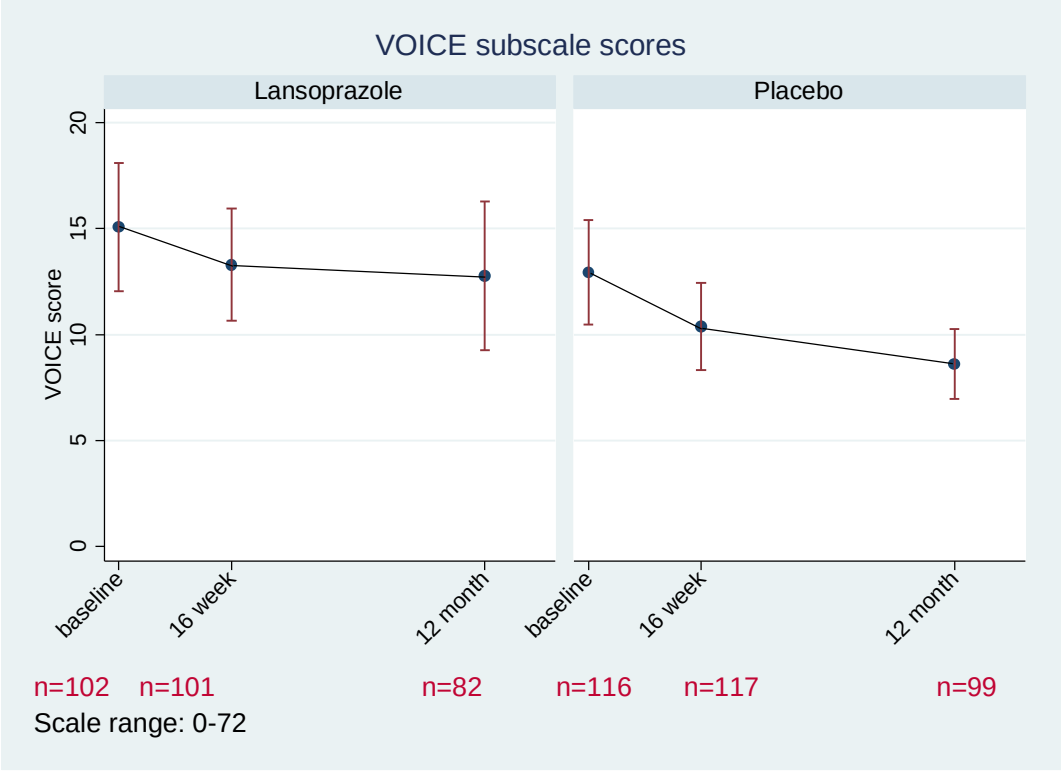

Figure 1 VOICE (LPR HRQL) subscale scores

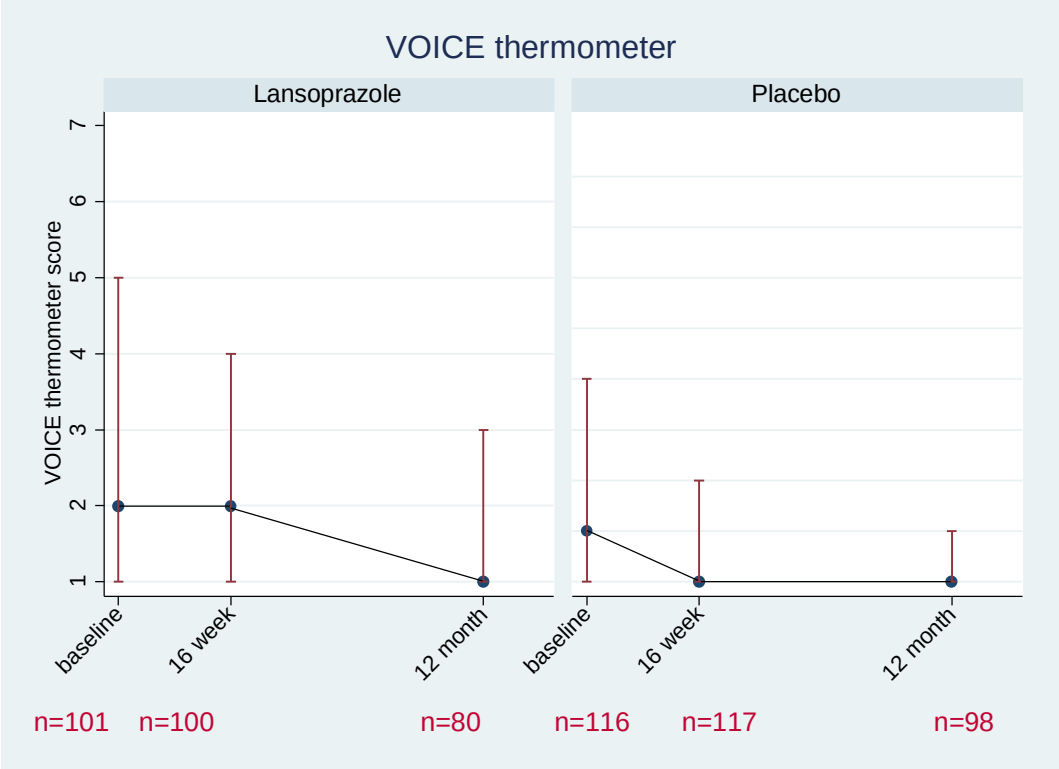

Figure 2: VOICE (LPR HRQL) thermometer scores

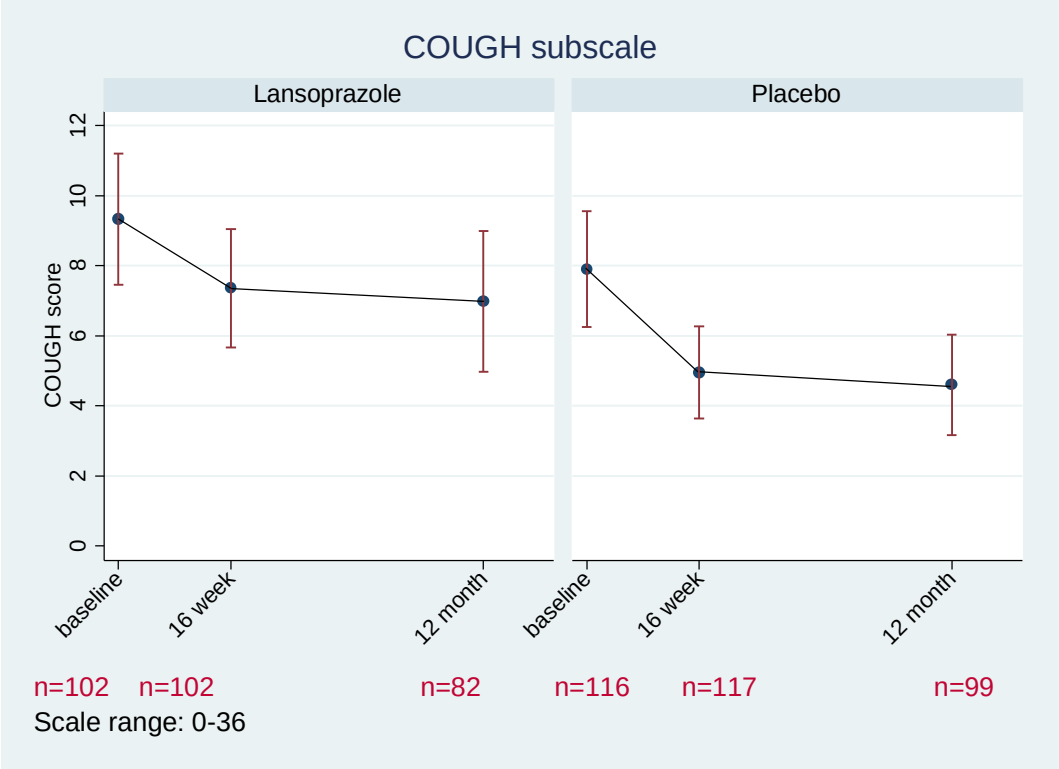

Figure 3: COUGH (LPR HRQL) subscale scores

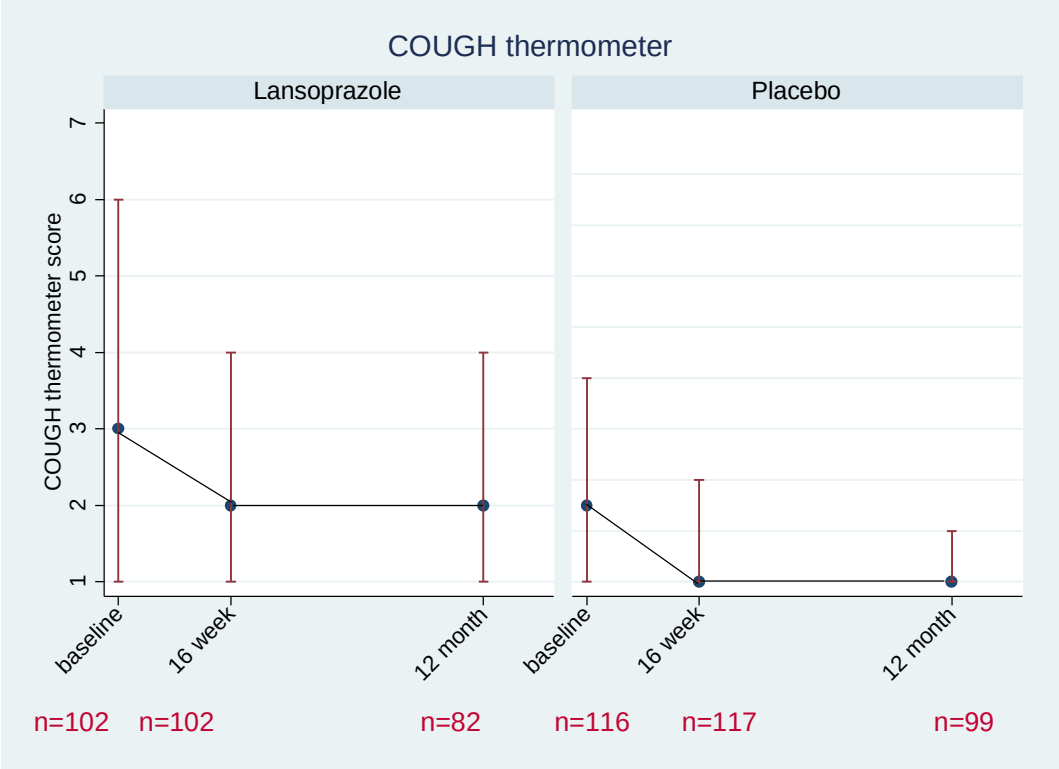

Figure 4: COUGH (LPR HRQL) thermometer scores

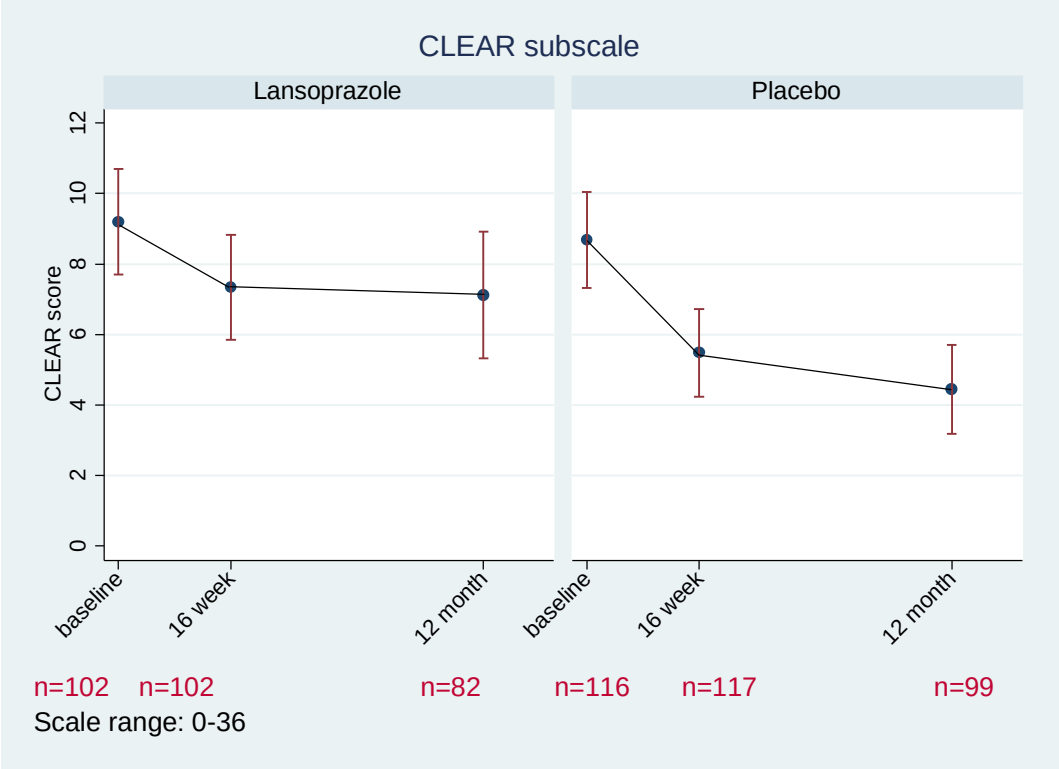

Figure 5: CLEAR (LPR HRQL) subscale scores

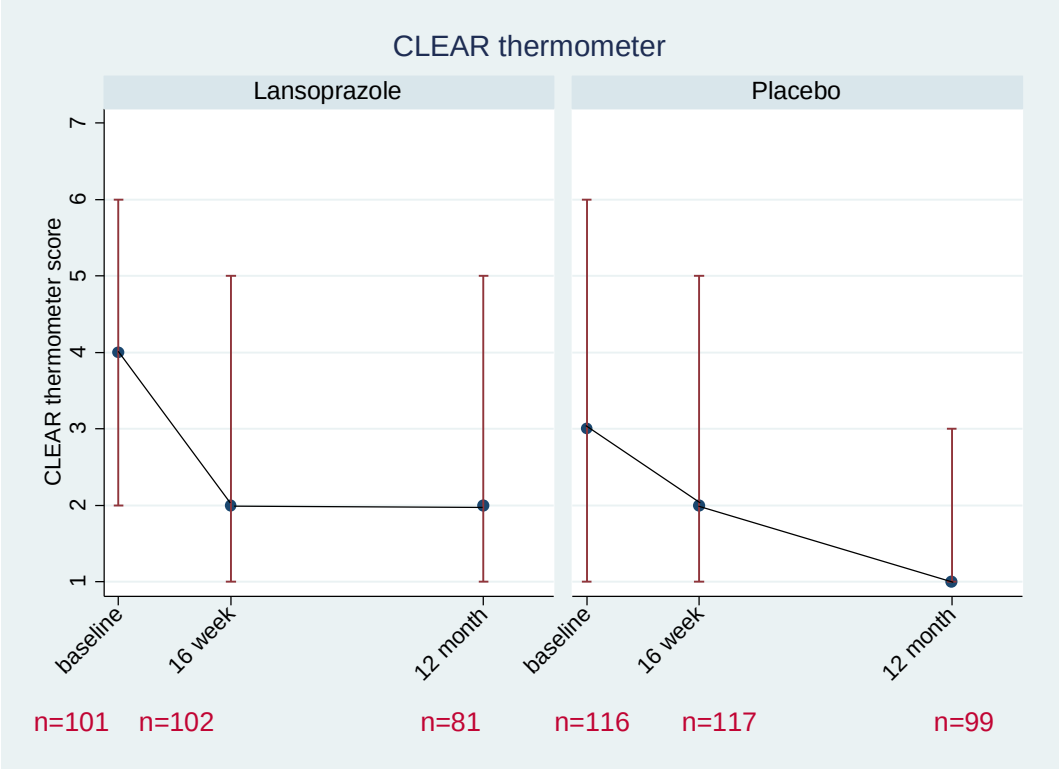

Figure 6: CLEAR (LPR HRQL) thermometer scores

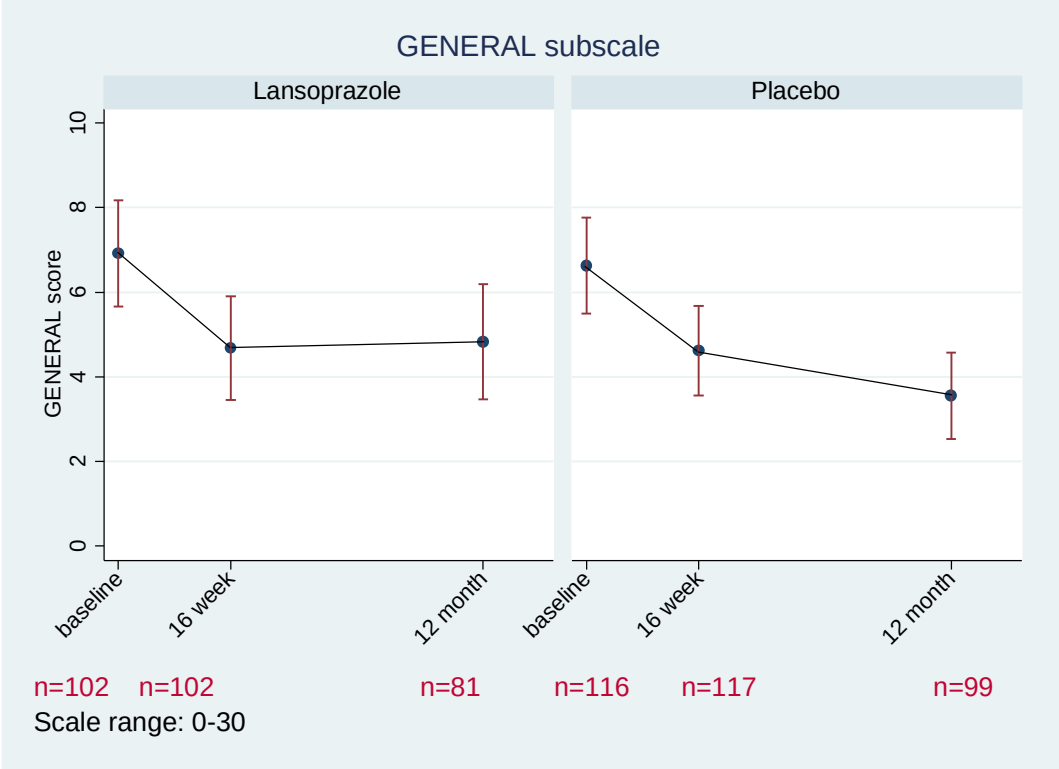

Figure 7: GENERAL (LPR HRQL) subscale scores

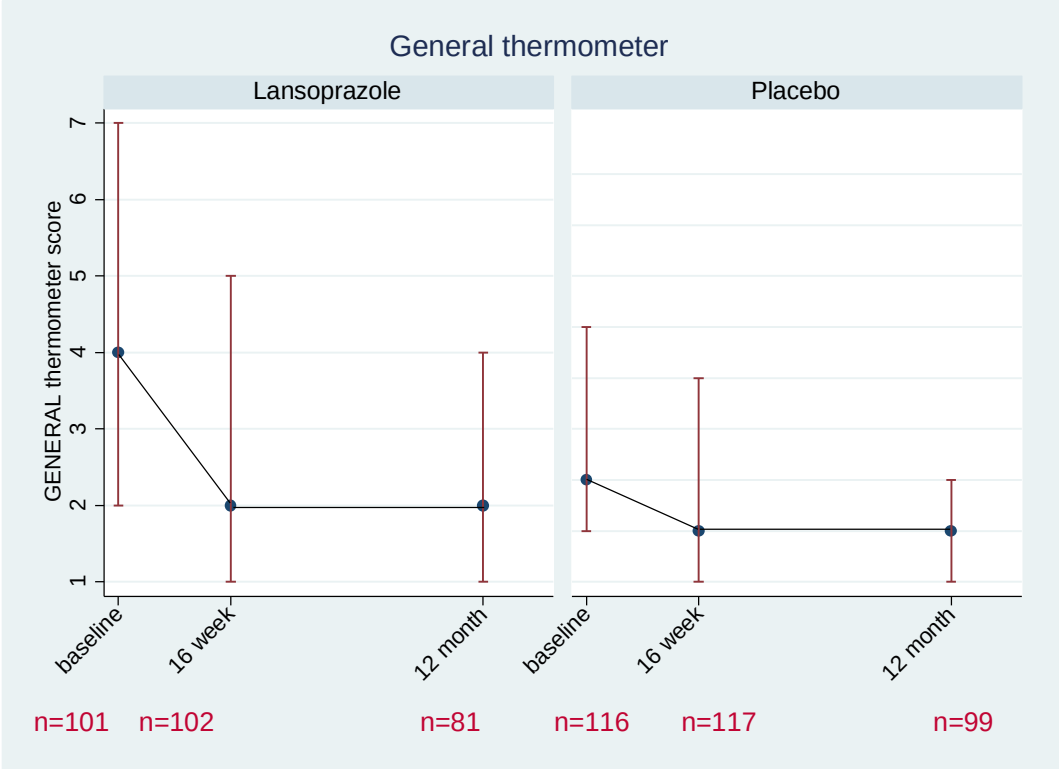

Figure 8: GENERAL (LPR HRQL) thermometer scores

Plots of laryngopharyngeal reflux health related quality of life (Domain scores)

Figures 9 to 18 show the LPR HRQL domain score graphs at baseline, 16 weeks and 12 months, showing median and interquartile range (scale range:1 to 10 shown on x axes). These domain scores along with the thermometer scores (figures 2, 4, 6 and 8) are used to calculate the overall score presented in Figure 16 of the main report.

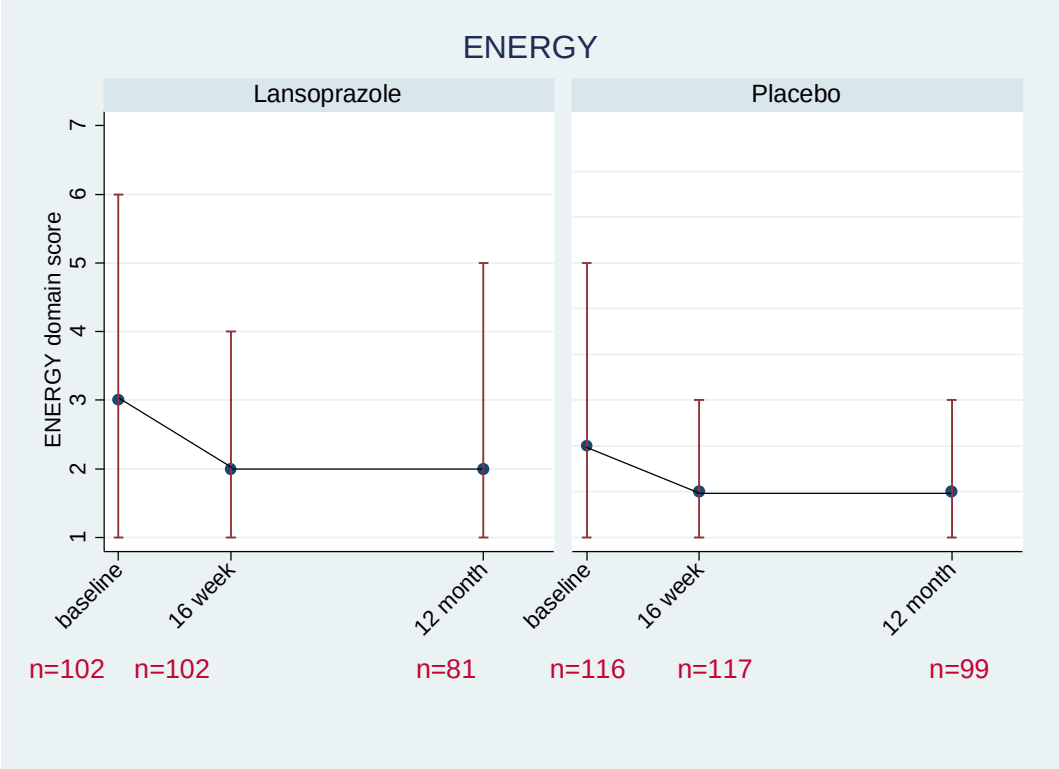

Figure 9: ENERGY domain scores (LPR HRQL)

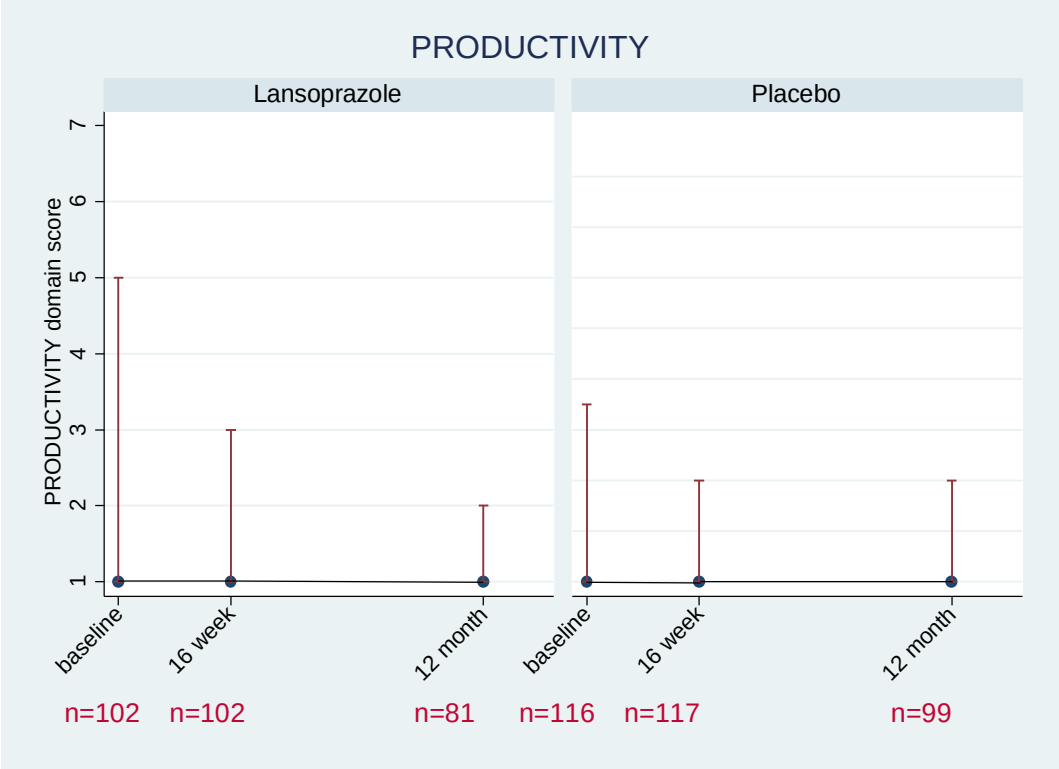

Figure 10: PRODUCTIVITY domain scores (LPR HRQL)

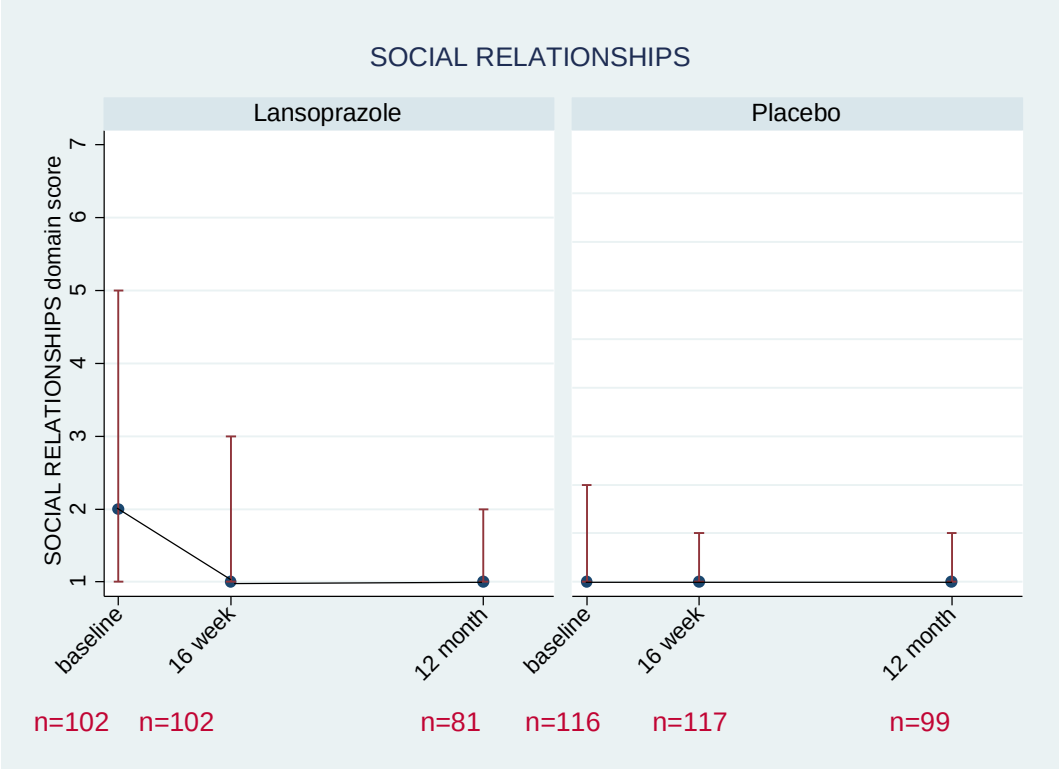

Figure 11: SOCIAL RELATIONSHIPS domain scores (LPR HRQL)

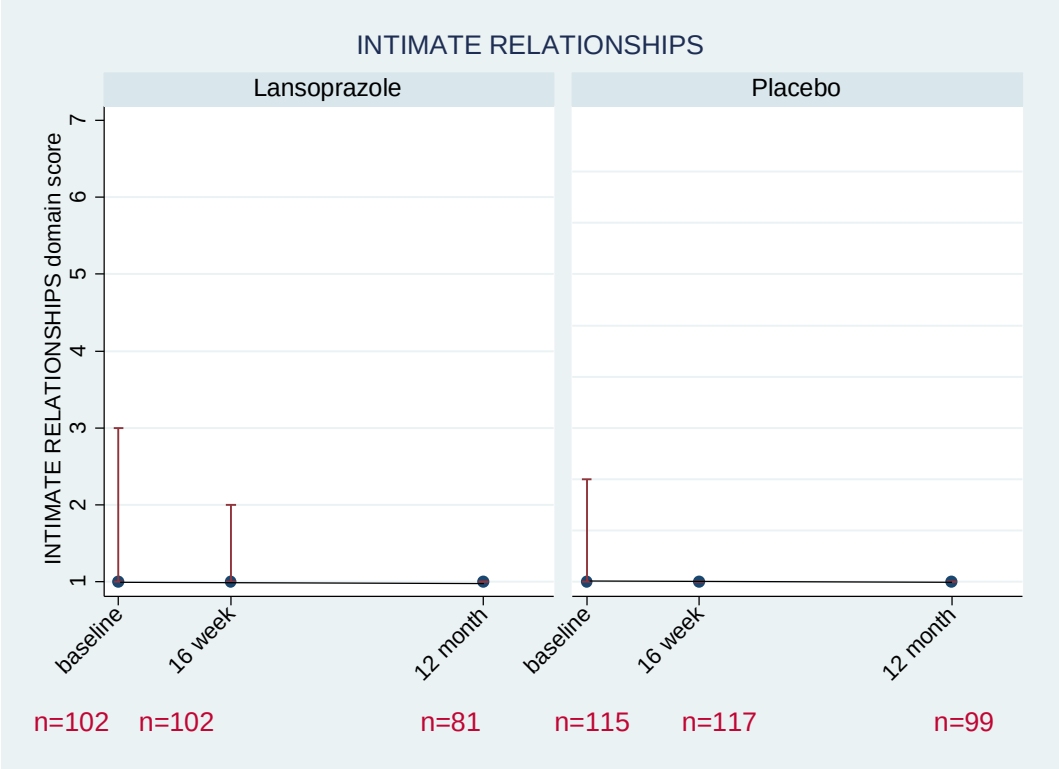

Figure 12: INTIMATE RELATIONSHIPS domain scores (LPR HRQL)

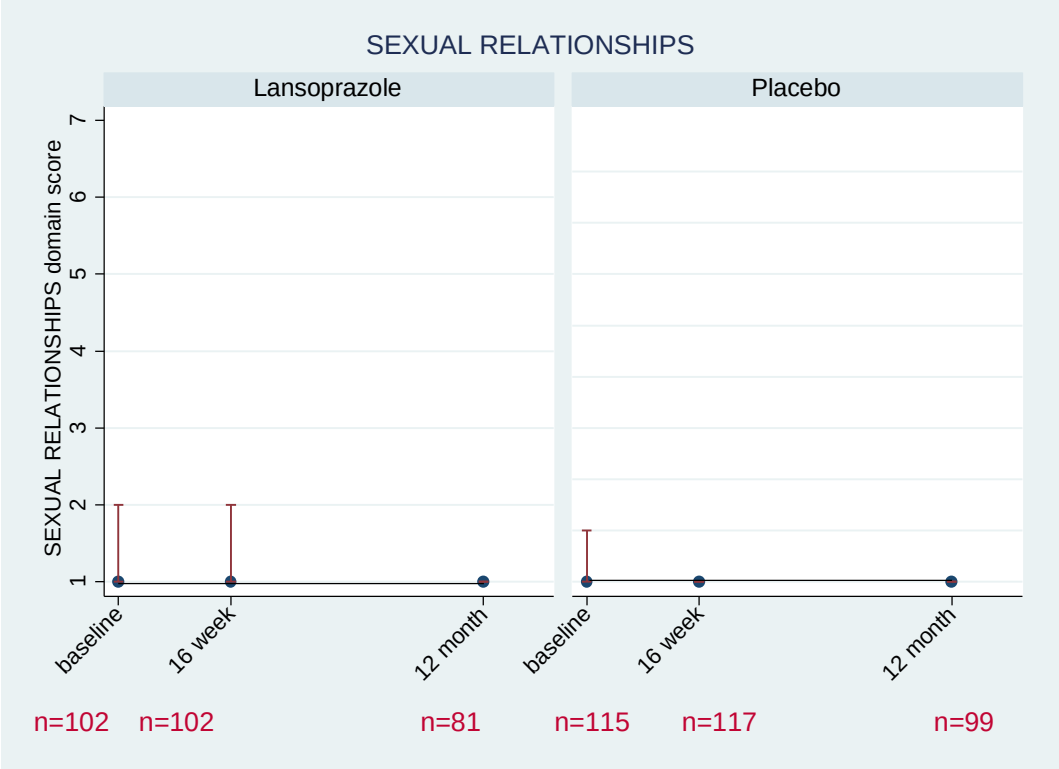

Figure 13: SEXUAL RELATIONSHIPS domain scores (LPR HRQL)

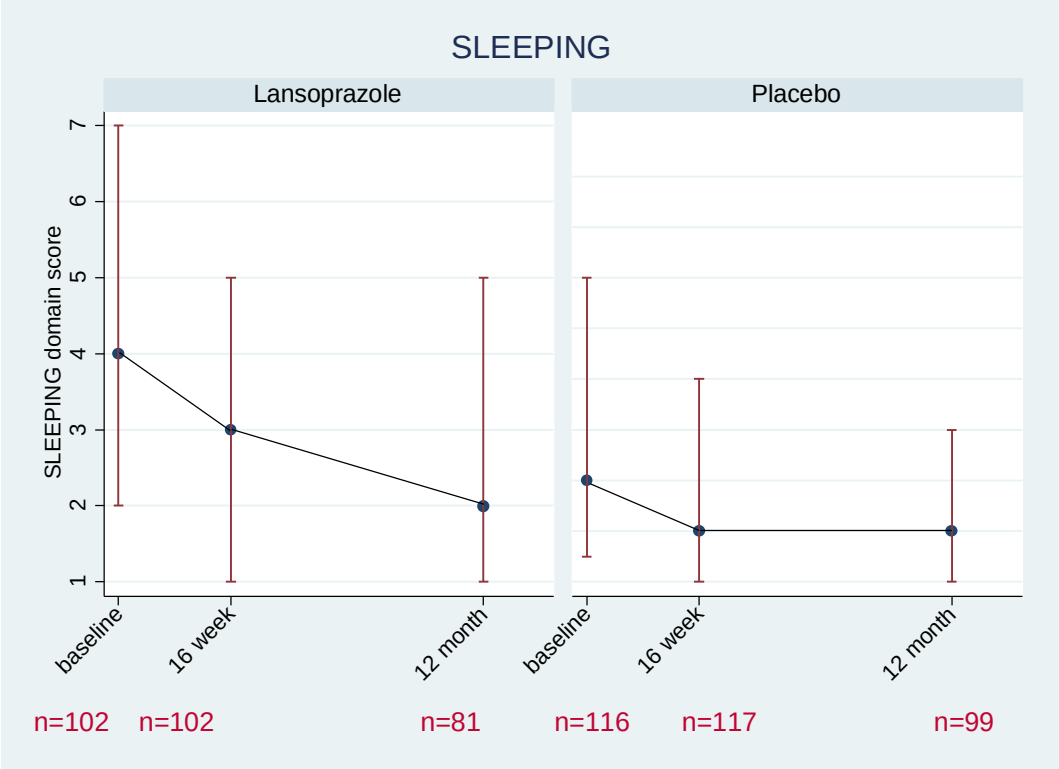

Figure 14: SLEEPING domain scores (LPR HRQL)

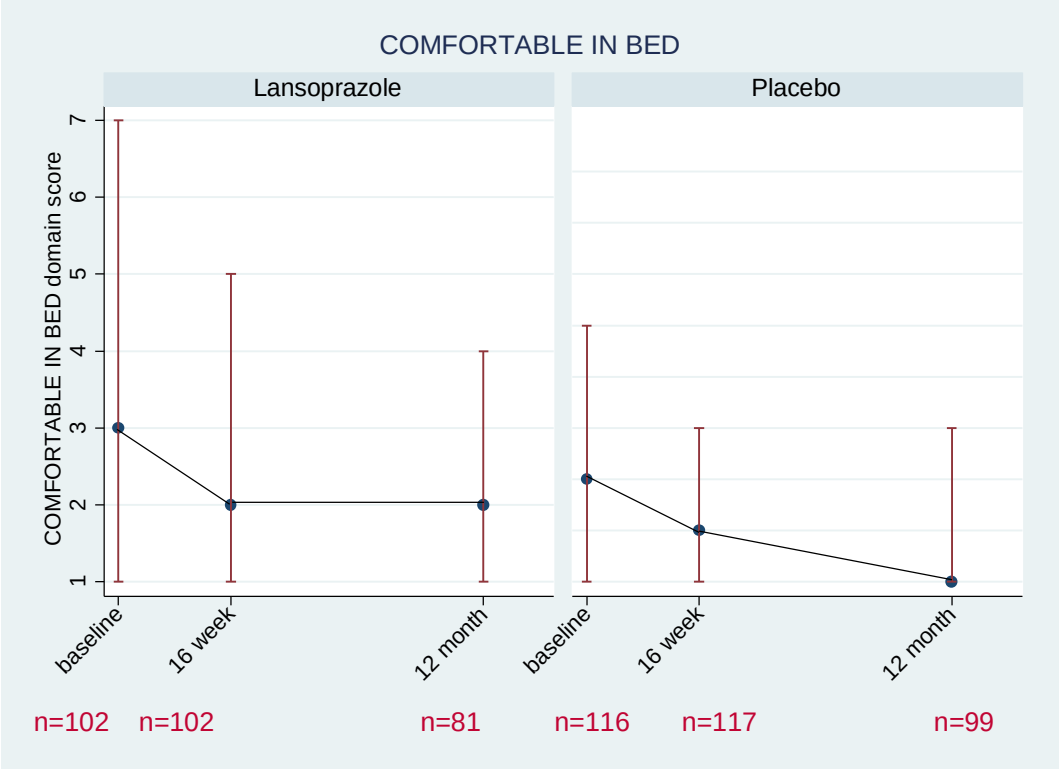

Figure 15: COMFORTABLE IN BED domain scores (LPR HRQL)

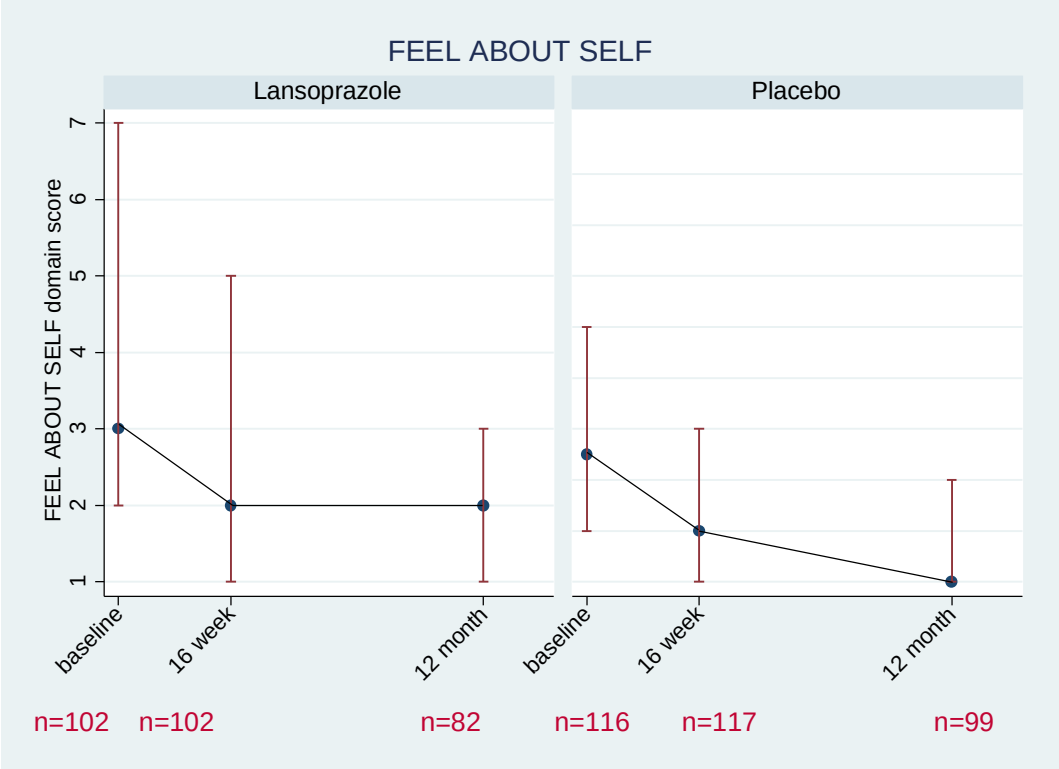

Figure 16: How FEEL ABOUT SELF domain scores (LPR HRQL)

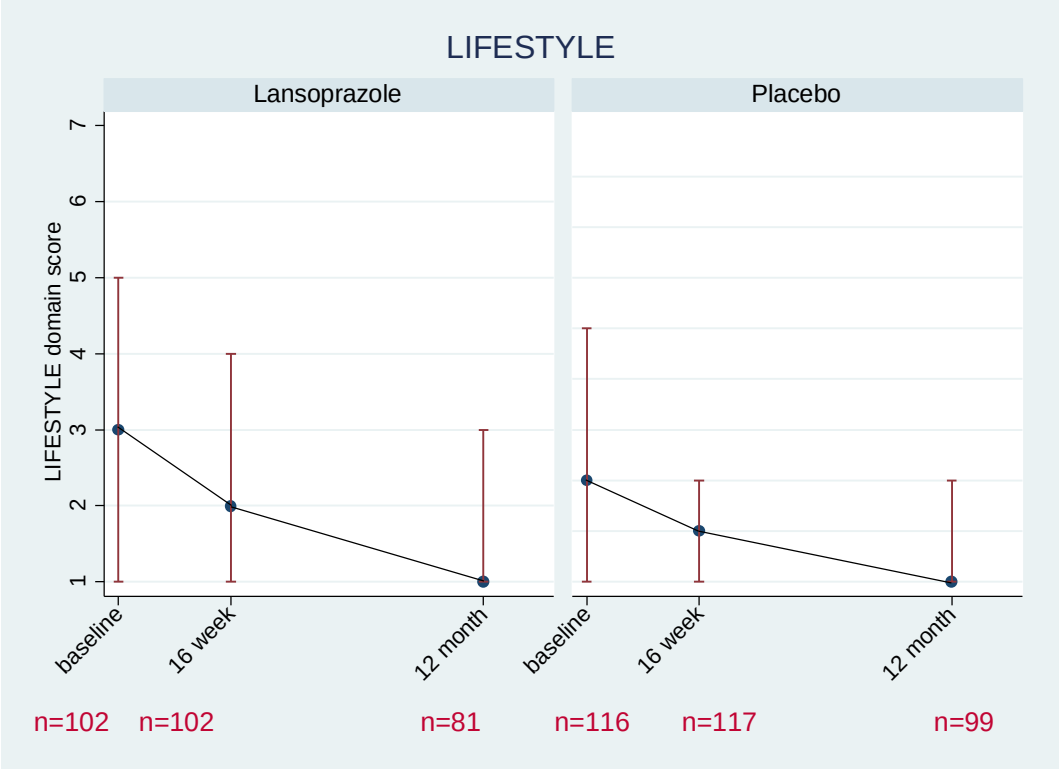

Figure 17: LIFESTYLE domain scores (LPR HRQL)

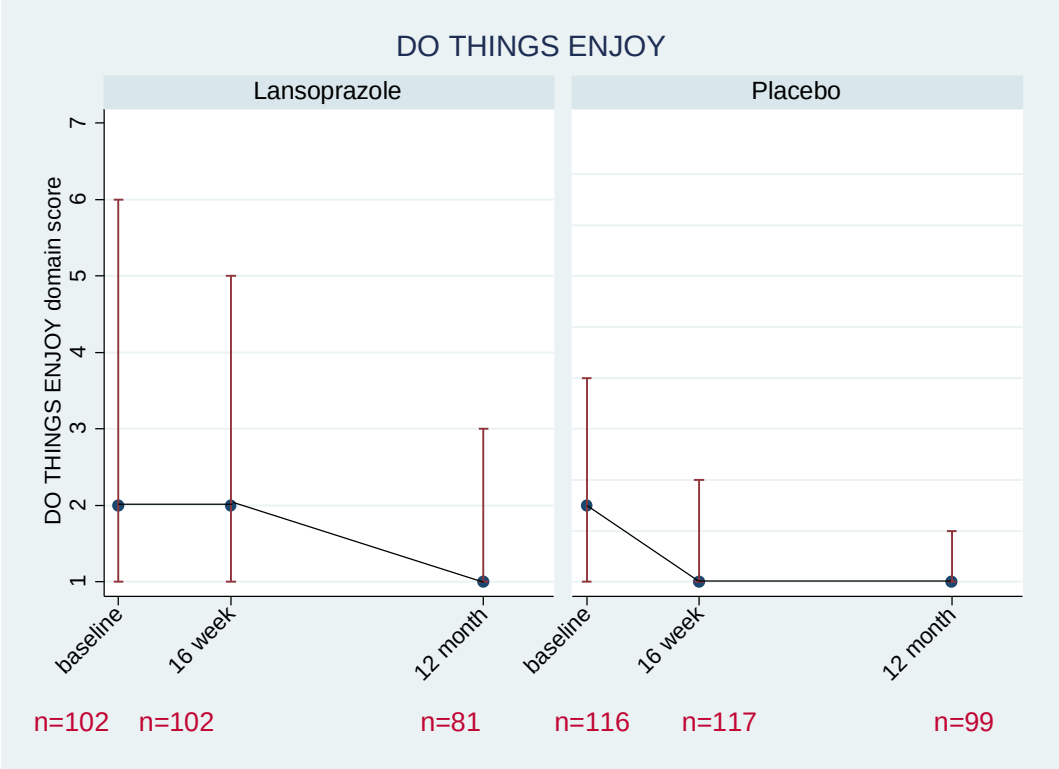

Figure 18: DO THINGS YOU ENJOY domain scores (LPR HRQL)