"Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosisd with Opioid Induced Constipation (OIC)"

Study NACASY

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Final Statistical Report

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1. HISTORY OF REVISION (Documentation of changes)

SECTIONS	VERSION	DATE REVISED	REVISED BY	DESCRIPTION OF CHANGES

INDEX

2. SYNOPSIS

2.1. Study title

"Open label, multinational, multicentre, prospective, real world observational study of Naloxegol for patients with cancer pain diagnosisd with Opioid Induced Constipation (OIC)"

2.2. Study Code

NACASY

2.3. Protocol Version and Amendments

Protocol version 2.0: 6th April 2018.

Protocol version 1.0: 6th February 2018.

2.4. Sponsor

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2.5. Design

This is a single-arm, open label, multinational, multicentre, prospective, real world observational study of Naloxegol in adult subjects with Opioid Induced Constipation (OIC) in patients receiving Naloxegol in routine clinical practice. Subjects who are receiving Naloxegol (prescribed by their physician according to the SmPC, which recommends that all currently used maintenance laxative therapy should be halted) during the enrolment period may be eligible for enrolment into the study.

2.6. Objectives

Primary:

The objective of this study is to assess the safety and efficacy of Naloxegol in a real world setting in cancer patients.

- The primary safety end point is the incidence of adverse events leading to study discontinuation.
- The primary efficacy end point is response rate during the 4 weeks treatment period. Response is defined as three or more bowel movements (without the use of rescue laxative treatment in the previous 24 hours) per week.

Secondary:

- Proportion of patients that have a BFI score change of ≥12 points at the end of the study treatment (4 weeks).
- Proportion of patients that have a BFI score <30 at the end of the study (patients adequately treated).
- Time to the first post-dose bowel movement.
- Change in stool consistency (Bristol stool scale).
- Change in Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL).
- Incidence of overall adverse events, including SAEs.
- Analgesic treatment interruptions/dose adjustments.
- Naloxegol treatment interruptions/dose adjustments.
- Patient satisfaction (PGI-I).

2.7. Inclusion Criteria

1. Patient ≥ 18 years old.
2. Patient with cancer pain.
3. Patient who is receiving treatment with opioids for at least 4 weeks, and is expected to remain on opioids for duration of study.
4. Patient with opioid induced constipation (OIC).
5. Patient in whom the clinician plans treatment with Naloxegol according to routine clinical practice (Naloxegol SmPC recommends that all currently used maintenance laxative therapy should be halted).
6. Signing of the informed consent.

2.8. Exclusion Criteria

1. Patients with colorectal cancer.

2.9. Study treatment

Naloxegol is a peripherally acting, μ-opioid receptor antagonist (PAMORA) that specifically targets the opioid receptor mechanisms responsible for OIC.

Naloxegol is indicated for the treatment of OIC in adult patients who have had an inadequate response to laxatives.

2.10. Total number of subjects

This study involved 170 patients (out-patients or in-patients) with OIC from 26 European hospitals.

3. GENERAL STATISTICAL CONSIDERATIONS

3.1. General principles

All descriptive statistics has been tabulated.

Categorical data has been summarized in tables presenting frequencies and percentages.

Continuous data has been summarized using the mean, median, standard deviation, range and Q1 and Q3. The number of non-evaluable outcomes and of missing data will have also been provided.

3.2. Handling of Missing Data

All available data has been included in data listings and tabulations.

4. STUDY POPULATIONS

4.1. Definition of study populations analysed

The following describes the different populations that have been used in the analyses process:

- **Efficacy population:** The efficacy analysis set has been the efficacy population, defined as all patients who meet all selection criteria, received at least 1 dose of study drug and have at least one post-baseline efficacy assessment.
- **Safety set:** The safety analysis set has been the Safety population, defined as all patients who meet all selection criteria and received at least 1 dose of study drug.

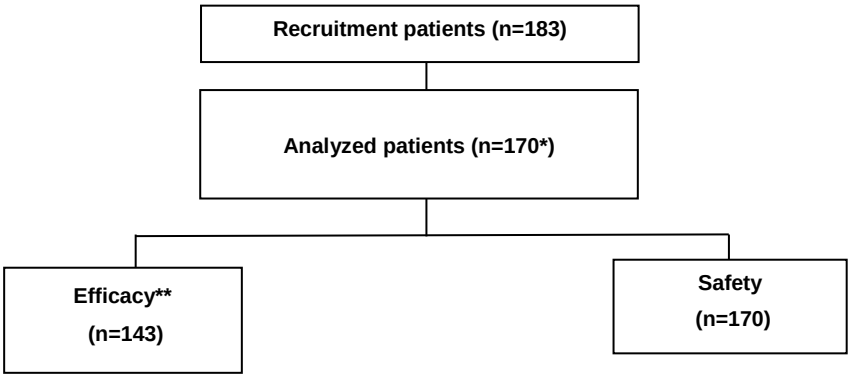
4.2. Study recruitment period.

The first patient inclusion date was 14/Aug/2018 and date of the last subject inclusion date was 31/Jan/2020.

4.3. Disposition of subjects

Study status

Figure 1: Disposition of subjects



*Screening failure:

Table 1: Screening failure

	Site N.	Site	Study Subject ID	Date	Reason
1	203	INSTITUT CATALÀ D'ONCOLOGIA BADALONA (ICO)	33139955*	2019-03-01	Patient does not meet criterion number 5: Naloxegol treatment not started.
2	304	AORN Dei Colli (Ospedale Monaldi)	33139998	2019-03-01	Patient does not meet inclusion criteria: Consent withdrawn (criterion 6)
3	202	COMPLEJO HOSPITALARIO DE NAVARRA	33140025	2019-03-29	Patient does not meet criterion number 5: Naloxegol treatment not started.
4	503	Gemma's Hospice	33140229	2019-04-22	Patient does not meet criterion number 5: Naloxegol treatment not started.
5	302	Mauriziano Hospital	33140330	2019-05-15	Patient does not meet criterion number 3: patient did not receive opioids for 4 weeks
6	404	Institut de Cancérologie de l'Oues (Paul Papin Angers)	33140642	2019-08-21	Patient does not meet criterion number 5: Naloxegol treatment not started.
7	404	Institut de Cancérologie de l'Oues (Paul Papin Angers)	33140798	2019-09-25	Patient does not meet criterion number 5: Naloxegol treatment not started.
8	403	Hopital Nord Amiens	33140833*	2019-09-20	Patient does not meet criterion number 5: Naloxegol treatment not started.
9	404	Institut de Cancérologie de l'Oues (Paul Papin Angers)	33140855	2019-11-18	Patient does not meet criterion number 5: Naloxegol treatment not started.
10	307	Ospedale A. Perrino	33141006	2020-02-05	Patient meets exclusion criteria: Colorectal cancer
11	307	Ospedale A. Perrino	33141067	2020-02-05	Patient meets exclusion criteria: Colorectal cancer
12	307	Ospedale A. Perrino	33141132	2020-02-05	Patient meets exclusion criteria: Colorectal cancer
13	307	Ospedale A. Perrino	33141133	2020-02-05	Patient meets exclusion criteria: Colorectal cancer

Table 2: Subjects per site

		N	%
Site	**Institut De Cancérologie De L'oues (Paul Papin Angers)**	26	15,3
	Aorn Dei Colli (Ospedale Monaldi)	22	12,9
	Palliative Care Unit "Jenny Karezi"	19	11,2
	Hopital Nord Amiens	19	11,2
	Ospedale A. Perrino	11	6,5
	Institut Català D'oncologia Badalona (Ico)	10	5,9
	Royal Surrey Hospital	8	4,7
	Hospital Universitari Vall D'hebron	8	4,7
	Rijnstate	5	2,9
	Hospital Del Mar	5	2,9
	Aalborg Universitets Hospital Farsø	5	2,9
	Tagesklinik Landshut	4	2,4
	Maastricht University Medical Centre	4	2,4
	Hospital Negrar	4	2,4
	Krebsheilkunde Lichtenberg	3	1,8
	Institut Gustave-Roussy	3	1,8
	Tampere University Hospital	2	1,2
	Institut De Cancérologie De L'ouest (Centre René Gauducheau)	2	1,2
	Hospital Clínico San Carlos	2	1,2
	Complejo Hospitalario De Navarra	2	1,2
	Skåne University Hospital	1	,6
	Hospital Universitario Fundación Jiménez Díaz	1	,6
	Gemma's Hospice	1	,6
	Chu Strasbourg	1	,6
	Chu Grenoble	1	,6
	Asst Fatebenefratelli Hospital	1	,6
	Total	170	100,0

** Efficacy population: patient received at least 1 dose of study drug and has information for visit 1 (baseline) and for at least one post-baseline visit.

Table 3: Naloxegol treatment

		N	%
Naloxegol initial dose	**25**	139	81,8
	12.5	30	17,6
	50	1	,6
	Total	170	100,0

Table 4: Subjects per visit

	N	%*
Visit 1 (week 1)	170	100,0
Visit 2 (week 2)	140	82,4
Visit 3 (week 4)	118	69,4

*Percentages calculated over total of evaluable patients (N=170).

The number of patient included in the efficacy population is 143. The reasons for patients not included are listed below:

Table 5: Reason for non- efficacy population

	StudySubjectID	Date Visit 1	Date (Early Discontinuation)	Reason (early discontinuation)	Reason (Non-efficacy population)
1	33139577	27-Nov-18	13-Dec-2018	Naloxegol adverse event	Information is only available for visit 1
2	33139664	15-Nov-18	12-Dec-2018	Lost follow-up	Information is only available for visit 1
3	33139734	20-Nov-18		Lost follow-up*	Information is only available for visit 1
4	33139931	11-Feb-19	18-Feb-19	Investigator's decision	Information is only available for visit 1
5	33139959	15-Feb-19	06-Mar-19	Adverse event	Information is only available for visit 1
6	33140093	18-Mar-19	28-Mar-19	Death	Information is only available for visit 1
7	33140105	25-Mar-19	26-Mar-19	Naloxegol adverse event	Information is only available for visit 1
8	33140125	20-Feb-19	07-Mar-19	Patient's decision	Information is only available for visit 1
9	33140153	03-Apr-2019	01-May-19	Death	Information is only available for visit 1
10	33140180	04-Apr-2019	06-Apr-2019	Adverse event	Information is only available for visit 1
11	33140185	01-Apr-2019	09-Apr-2019	Naloxegol adverse event	Information is only available for visit 1
12	33140186	08-Apr-2019	09-Apr-2019	Naloxegol adverse event	Information is only available for visit 1
13	33140306	10-May-19	11-May-19	Naloxegol adverse event	Information is only available for visit 1
14	33140557	19-Jun-19	27-Jun-19	Patient's decision	Information is only available for visit 1
15	33140604	01-Jul-19	05-Jul-19	Adverse event	Information is only available for visit 1
16	33140752	19-Jun-19	05-Jul-19	Consent withdrawn	Information is only available for visit 1
17	33140190	10-Apr-2019	23-Apr-2019	Naloxegol adverse event	Information is only available for visit 1
18	33140273	03-May-2019	17-May-2019	Patient's decision	Information is only available for visit 1
19	33141125	19-Nov-2019	25-Nov-2019	Investigator's decision	Information is only available for visit 1
20	33140835	14-Oct-2019	18-Oct-2019	Investigator's decision	Information is only available for visit 1
21	33140567	18-Jun-2019	23-Jun-2019	Naloxegol adverse event	Information is only available for visit 1
22	33140814	04-Oct-19	07-Oct-19	Patient's decision	Information is only available for visit 1
23	33140819	07-Oct-19	14-Oct-19	Investigator's decision	Information is only available for visit 1
24	33140932	20-Nov-19	25-Nov-19	Death	Information is only available for visit 1
25	33140996	02-Dec-2019	26-Dec-2019	Lost follow-up	Information is only available for visit 1
26	33141137	28-Jan-2020	11-Feb-20	Lost follow-up	Information is only available for visit 1
27	33141152	29-Jan-2020	13-Feb-20	Patient's decision	Information is only available for visit 1

*Patient 33139734 has not completed "Early discontinuation" form. Information verified during a monitoring visit.

Table 6: Subjects per site (efficacy population)

	N	%
Institut De Cancérologie De l'Oues (Paul Papin Angers)	24	16,8
Aorn Dei Colli (Ospedale Monaldi)	20	14,0
Palliative Care Unit "Jenny Karezi"	18	12,6
Hopital Nord Amiens	16	11,2
Ospedale A. Perrino	9	6,3
Royal Surrey Hospital	7	4,9
Institut Català D'oncologia Badalona (Ico)	7	4,9
Hospital Universitari Vall D'hebron	5	3,5
Rijnstate	4	2,8
Hospital Negrar	4	2,8
Aalborg Universitets Hospital Farsø	4	2,8
Tagesklinik Landshut	3	2,1
Maastricht University Medical Centre	3	2,1
Krebsheilkunde Lichtenberg	3	2,1
Institut Gustave-Roussy	3	2,1
Tampere University Hospital	2	1,4
Institut De Cancérologie De l'Ouest (Centre René Gauducheau)	2	1,4
Hospital Del Mar	2	1,4
Hospital Clínico San Carlos	2	1,4
Skåne University Hospital	1	,7
Hospital Universitario Fundación Jiménez Díaz	1	,7
Complejo Hospitalario De Navarra	1	,7
Chu Grenoble	1	,7
Asst Fatebenefratelli Hospital	1	,7
Total	143	100,0

4.4. Study Discontinuations

Table 7: Study discontinuations

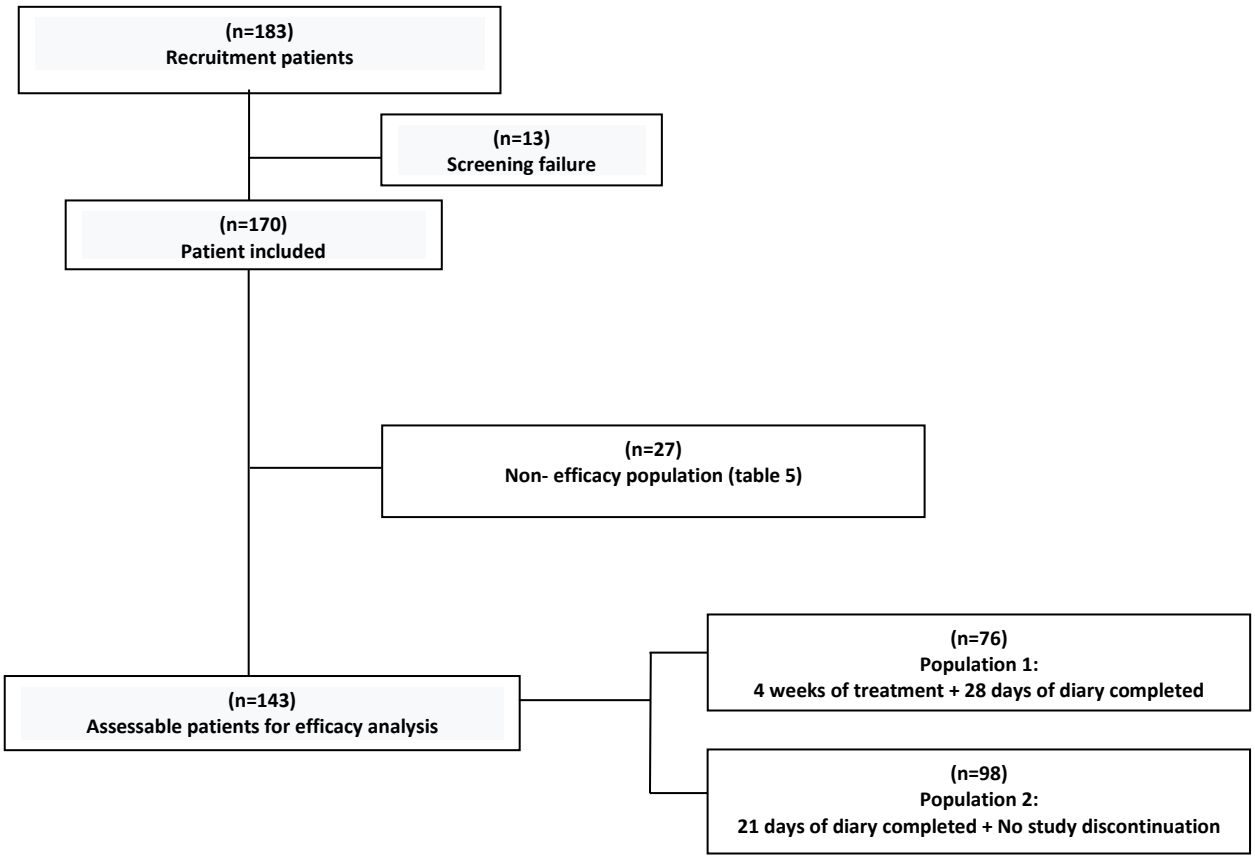
	N	%
Naloxegol Adverse Reaction	12	21,4
Patient decision	10	17,9
Adverse event	8	14,3
Death	7	12,5
Lost follow-up	7	12,5
Investigator decision	6	10,7
Consent withdrawn	6	10,7
Total	56	100,0

Table 8: Patient study discontinuations description

		Discontinuation reason	Population
1	**33139577**	Naloxegol Adverse Reaction: Abdominal pain (patient in treatment with metadona). Grade: moderate	Safety population
2	**33139637**	Investigator decision: pain not well controled and opioids were ceased. Then, Naloxegol was stopped. Thanks.	Safety and efficacy population
3	**33139639**	Consent withdrawn	Safety and efficacy population
4	**33139652**	Consent withdrawn	Safety and efficacy population
5	**33139655**	Consent withdrawn	Safety and efficacy population
6	**33139656**	Consent withdrawn	Safety and efficacy population
7	**33139664**	Lost follow-up: last date 14-NOV-2018	Safety population
8	**33139733**	Consent withdrawn	Safety and efficacy population
9	**33139762**	Naloxegol Adverse Reaction: abdominal pain and nausea. Grade: moderate	Safety and efficacy population
10	**33139931**	Investigator decision: efficacy loss	Safety population
11	**33139959**	Adverse event: Oncologic pain. Grade: severe	Safety population
12	**33139981**	Naloxegol Adverse Reaction: Diarrhea. Grade UNK	Safety and efficacy population
13	**33140023**	Death (cancer)	Safety and efficacy population
14	**33140093**	Death (cancer)	Safety population
15	**33140105**	Naloxegol Adverse Reaction: Intestinal perforation. Grade: severe	Safety population
16	**33140125**	Patient decision	Safety and efficacy population
17	**33140135**	Investigator decision: Low efficacy (no defecation under 25mg Naloxegol)	Safety and efficacy population
18	**33140153**	Death (cancer)	Safety and efficacy population
19	**33140179**	Adverse event: progression of disease. Grade: severe	Safety and efficacy population
20	**33140180**	Adverse event: suicide. Grade: severe	Safety population
21	**33140185**	Naloxegol Adverse Reaction: abdominal pain. Grade: moderate	Safety population
22	**33140186**	Naloxegol Adverse Reaction: abdominal pain. Grade: moderate	Safety population
23	**33140190**	Naloxegol Adverse Reaction: abdominal pain. Grade: moderate	Safety and efficacy population
24	**33140213**	Patient decision	Safety and efficacy population
25	**33140223**	Lost follow-up: last date 08-MAY-2019	Safety and efficacy population
26	**33140237**	Patient decision	Safety and efficacy population
27	**33140259**	Patient decision	Safety and efficacy population
28	**33140273**	Patient decision	Safety and efficacy population
29	**33140306**	Naloxegol Adverse Reaction: Abdominal cramps. Grade: unknown	Safety population
30	**33140337**	Adverse event: progression. Grade: unknown	Safety and efficacy population
31	**33140458**	Naloxegol Adverse Reaction: fatigue. Grade: moderate	Safety and efficacy population
32	**33140557**	Patient decision	Safety population
33	**33140567**	Naloxegol Adverse Reaction: diarrhea. Grade: moderate	Safety and efficacy population
34	**33140594**	Death (cancer)	Safety and efficacy population
35	**33140604**	Adverse event: disease progression. Grade: severe	Safety population
36	**33140676**	Adverse event: Coma. Grade: severe	Safety and efficacy population
37	**33140704**	Patient decision	Safety and efficacy population
38	**33140712**	Adverse event: Diarrhea. Grade : severe	Safety and efficacy population
39	**33140752**	Consent withdrawn	Safety population
40	**33140760**	Naloxegol Adverse Reaction: Severe abdominal cramps. Grade: severe	Safety and efficacy population
41	**33140792**	Death (cancer)	Safety and efficacy population
42	**33140800**	Naloxegol Adverse Reaction: abdominal colic. Grade: mild	Safety and efficacy population
43	**33140804**	Lost follow-up: last date 16-OCT-2019	Safety population
44	**33140814**	Patient decision	Safety population
45	**33140819***	Investigator decision: Severe clinical deterioration due to progression	Safety population

		Discontinuation reason	Population
		of cancer disease. Inability to take oral medication	
46	**33140820**	Patient decision	Safety and efficacy population
47	**33140835**	Investigator decision: subject opening bowels without naloxegol	Safety population
48	**33140932**	Death (cancer)	Safety population
49	**33140996**	Lost follow-up: last date 26-DEC-2019	Safety population
50	**33141125**	Investigator decision: Due to the new chemotherapy therapy initiated by the patient, it was decided to discontinue Naloxegol.	Safety population
51	**33141127**	Adverse event: vertigo. Grade: unknown	Safety and efficacy population
52	**33141136**	Death (cancer)	Safety and efficacy population
53	**33141137**	Lost follow-up: last date 11-FEB-2020	Safety population
54	**33141152**	Patient decision	Safety population
55	**33140995**	Lost follow-up	Safety and efficacy population
56	**33139734**	Lost follow-up	Safety population

Figure 5: Disposition of subjects II



4.5. Deaths

Table 9: Death (safety population)

		N	%
Death reason	**Cancer**	21	84,0
	Adverse event [1]	3	12.0
	Naloxegol adverse reaction [2]	1	4,0
	Total	25	100,0

[1]Patients:
- 33140194: pneumopathy.
- 33140179: progression disease.
- 33140180: suicide.

[2] Patient 33140105: Intestinal perforation.

5. SUBJECT DESCRIPTION

5.1. Demographic and baseline description. General considerations

The demographic and baseline description have been performed for efficacy population (N=143).

5.2. Subject characteristics

Table 10: Gender

		N	%
Gender	**Female**	78	54,5
	Male	65	45,5
	Total	143	100,0

Table 11: Race

		N	%
Racer	**Caucasian**	116	81,1%
	Other*	26	18,2%
	Arab	1	0,7%
	Total	143	100,0%

*All cases that indicated other specified "Not applicable in France".

Table 12: Age, height and weight

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Age	143	64,1	58,0	66,0	72,0	12,4	21,0	92,0
Height	143	165,9	160,0	165,5	171,0	8,3	142,0	187,0
Weight*	143	68,6	58,0	66,0	78,0	13,5	45,0	110,0

5.3. Cancer characteristics

Table 13: Tumor location

		N	%
Tumor location	**Other**	57	39,9
	Lung	35	24,5
	Breast	32	22,4
	Prostate	12	8,4
	Uterus	4	2,8
	Kidney	3	2,1
	Other		
	Pancreas	10	7,0
	Bladder	6	4,2
	Head and neck	5	3,5
	Bone	3	2,1
	Ovarian	2	1,4
	Tongue	2	1,4
	Adrenal	1	0,7
	Base of tongue	1	0,7
	Bile duct	1	0,7
	Biliary	1	0,7
	Cervix	1	0,7
	Chordoma	1	0,7
	Esophagus	1	0,7
	Esophagus and larynx	1	0,7
	Forehead	1	0,7
	Gastric	1	0,7
	Hypopharynx	1	0,7
	Lambda light chains in multiple myeloma	1	0,7
	Left cervical	1	0,7
	Left cheek	1	0,7
	Leukemia	1	0,7
	Melanom	1	0,7
	Multiple myeloma	1	0,7
	Myeloma	1	0,7
	Non hodgkin lymphoma	1	0,7
	Oral cavity	1	0,7
	Oropharynx	1	0,7
	Paravertebral	1	0,7
	Retroperitoneal	1	0,7
	Testicle	1	0,7
	Thigh	1	0,7
	Thyroid cancer	1	0,7
	Unknown	1	0,7
	Urothelial carcinoma	1	0,7
	Waldestrom	1	0,7
	Total	143	100,0

Table 14: Presence of metastasis

		N	%
Metastasis	**No**	44	30,8
	Yes	99	69,2
	Total	143	100,0

Table 15: Metastatic location per patient

		N	%*
Metastatic location	**Bone**	29	29,3
	Lymph Nodes	12	12,1
	Liver	7	7,1
	Bone + Liver	6	6,1
	Bone + Lymph Nodes	5	5,1
	Bone + Brain	3	3,0
	Lung	3	3.0
	Bone + Lung	2	2,0
	Brain	2	2,0
	Bone + Lungs + Lymph Nodes	2	2,0
	Lung + Lymph Node	2	2,0
	Spine	2	2,0
	Adrenal Glands	2	2,0
	Bone + Lung + Lymph Nodes + Abdomen	1	1,0
	Bone + Pulmonary + Cerebral	1	1,0
	Brain + Bone + Liver	1	1,0
	Breast Bilateral + Lymph nodes + Bone	1	1,0
	Cerebellum + Adrenal Glands + Lymph Nodes	1	1,0
	CNS + Plexus Choroideus	1	1,0
	Ganglion	1	1,0
	Ganglion + Liver + Bone	1	1,0
	Bowel	1	1,0
	Liver + Bone + Lymph Nodes	1	1,0
	Liver + Lung + Lymph Nodes	1	1,0
	Lung + Brain + Bones	1	1,0
	Lung + Liver	1	1,0
	Lung + Liver + Abdomen	1	1,0
	Lung + Lymph Nodes + Bone + Abdomen	1	1,0
	Lymph Node + Hepatic + Pleural + Lung	1	1,0
	Mediastinum	1	1,0
	Peritoneal + Liver Lymph Nodes	1	1,0
	Peritoneo	1	1,0
	Pulmonary + Peritoneum	1	1,0
	Skin + Lymph Nodes	1	1,0
	Tonsil	1	1,0
	Bone + Liver	1	1,0
	Total	99	100

*Percentages have been calculated over total of patient with metastasis.

Table 16: Metastatic location (regrouped)

		N	%
Metastatic locations	**Bone**	61	61,6
	Lymph Nodes	31	31,3
	Lung	22	22,2
	Liver	19	19,2
	Brain	9	9,1
	Adbdomen	6	6,1
	Adrenal Glands	3	3,0
	Bowel	1	1,0
	Breast Bilateral	1	1,0
	CNS	1	1,0
	Mediastinum	1	1,0
	Skin	1	1,0
	Spine	1	1,0
	Tonsil	1	1,0
	Plexus Choroideus	1	1,0

*Percentages have been calculated over total of patient with metastasis.

Table 17: Current chemotherapy treatment

		N	%
Current chemotherapy treatment	**No**	77	53,8
	Yes	66	46,2
	Total	143	100,0

Table 18: Current chemotherapy treatment description

		N	%
Current chemotherapy treatment description	**Nivolumab**	4	6,1
	Capecitabine	3	4,5
	Carboplatin + Gemcitabine	3	4,5
	Carboplatin + Paclitaxel	2	3,0
	Docetaxel	2	3,0
	Nab-Paclitaxel + Gemcitabine	2	3,0
	Pemetrexed	1	1,5
	Alpelisib/Placebo + Fulvestrant	1	1,5
	Bevacizumab + Selicrelumab	1	1,5
	Cabacitaxel	1	1,5
	Capecitabine + Lapatinib	1	1,5
	Capecitabine And Zoledronic Acid	1	1,5
	Carboplatin + Pemetrexed	1	1,5
	Carboplatin + Nab-Paclitaxel	1	1,5
	Carboplatin	1	1,5
	Carboplatin + Paclitaxel	1	1,5
	Carboplatin + Etoposide	1	1,5
	Carboplatin + Gemcitabine	1	1,5
	Carboplatin + Vp16	1	1,5
	Cetuximab	1	1,5
	Cisplatin + 5-FU	1	1,5
	Cisplatin + Pemetrexed	1	1,5
	Daratumumab	1	1,5
	Denosumab + Enzalutamide	1	1,5
	Docetaxel + Carboplatin + 5-FU	1	1,5
	Docetaxel +Trastuzumab + Pertuzumab	1	1,5
	Endoxan	1	1,5
	Folfirinox	1	1,5
	Gemcitabine + Abraxane	1	1,5
	Gemcitabine + Carboplatin	1	1,5
	Gemcitabine + Nab-Paclitaxel	1	1,5
	Gemcitabine + Cisplatin	1	1,5
	Ifosfamide	1	1,5

		N	%
	Pomalidomide	1	1,5
	Lenalidomide	1	1,5
	Methotrexate	1	1,5
	Paclitaxel + Pertuzumab + Trastuzumab	1	1,5
	Paclitaxel	1	1,5
	Palbociclib + Fulvestrant	1	1,5
	Pembrolizumab + Carboplatin	1	1,5
	Platinum + Paclitaxel	1	1,5
	Docetaxel	1	1,5
	Cisplatin	1	1,5
	Paclitaxel + ifosfamide + cisplatin	1	1,5
	Topotecan	1	1,5
	Vinorelbine	1	1,5
	Not available*	11	16,7
	Total	66	100,0

Table 19: Current radiotherapy treatment

		N	%
Current radiotherapy treatment	**No**	124	86,7
	Yes	19	13,3
	Total	143	100,0

Table 20: Current chemotherapy and radiotherapy treatment

		N	%
Current chemotherapy and radiotherapy treatment	**No**	130	90,9
	Yes	13	9,1
	Total	143	100,0

5.4. Pain treatment

Table 21: Patient with opioid treatment for more than 1 month

		N	%
Opioid treatment for more than 1 month	**Yes**	143	100,0
	Total	143	100,0

Visit 1 (week 1)

Table 22: Opioid treatment at visit 1

		N	%
Opioid treatment	**Fentanyl**	38	26,6
	Oxycodone	36	25.2
	Other*	24	66.7
	Morphine	16	16.8
	Oxycodone/Naloxone	10	7,0
	Hydromorphone	8	5,6
	Tramadol	6	4,2
	Codeine	4	2,8
	Tapentadol	1	,7
	Total	143	100,0

*Other opioid treatments are listed in table 25.

Table 23: Other opioid treatment at visit 1

		N	%
Other opioid treatment	**Methadone**	7	4,9
	Codeine/paracetamol	4	2,8
	Codeine/paracetamol /caffeine	3	2,1
	Fentanyl + Morphine	2	1,4
	Tramadol/paracetamol	2	1,4
	Fentanyl + Methadone	1	,7
	Hydromorphine + Morphine	1	,7
	Hydromorphine + Oxycodone	1	,7
	Methadone/Tapentadol	1	,7
	Morphine + methadone	1	,7
	Oxycodone/paracetamol	1	,7
	Total	24	16,8

Table 24: Other pain treatment at visit 1

		N	%
Other pain treatment	**No**	43	30,1
	Yes	100	69,9
	Total	143	100,0

Table 25: Other pain treatment (specify) at visit 1

		N	%**	%***
Other pain treatment	**Paracetamol**	19	19,0	13,3
	Anti-convulsants	17	17,0	11,9
	Antidepressants+Anti-convulsants	10	10,0	6,9
	Corticoids+Anti-convulsants	7	7,0	4,9
	Antidepressants	6	6,0	4,2
	Antidepressants+Paracetamol	5	5,0	3,5
	Other*	5	5,0	3,5
	NSAIDs	4	4,0	2,8
	Neuroleptics+Paracetamol	3	3,0	2,1
	Antidepressants+Other (anesthetic (Versatis))	2	2,0	1,4
	Antidepressants+Paracetamol+Anti-convulsants	2	2,0	1,4
	Paracetamol+Anti-convulsants	2	2,0	1,4
	Paracetamol+NSAIDs	2	2,0	1,4
	Anti-convulsants+Other (anesthesic)	1	1,0	0,7
	Antidepressants+NSAIDs	1	1,0	0,7
	Biphosphonates+Anti-convulsants	1	1,0	0,7
	Corticoids	1	1,0	0,7
	Corticoids+Antidepressants+Anti-convulsants	1	1,0	0,7
	Corticoids+Neuroleptics	1	1,0	0,7
	Corticoids+Neuroleptics+Antidepressants+Paracetamol+NSAIDs	1	1,0	0,7
	Corticoids+Paracetamol	1	1,0	0,7
	Corticoids+Paracetamol+Anti-convulsants+Other (metamizol)	1	1,0	0,7
	Neuroleptics	1	1,0	0,7
	Neuroleptics+Anti-convulsants	1	1,0	0,7
	Neuroleptics+Antidepressants	1	1,0	0,7
	Neuroleptics+Antidepressants+Anti-convulsants	1	1,0	0,7
	Neuroleptics+Antidepressants+Paracetamol+NSAIDs+Anti-convulsants	1	1,0	0,7
	Neuroleptics+Paracetamol+NSAIDs+Other (metamizol)	1	1,0	0,7
	Paracetamol+Other (nefopam (analgesics))	1	1,0	0,7
	Total	100	100,0	69,9

*Other pain treatment: 1 hypnotic and 4 metamizol.
**Percentages have been calculated over total with other pain treatment (N=100).
***Percentages have been calculated over total of patient (N=143).

Table 26: Number of patient by pain treatment at visit 1

		N	%*
Other pain treatment	**Anti-convulsants**	45	31,5
	Paracetamol	39	27,3
	Antidepressants	31	21,7
	Corticoids	13	9,1
	Neuroleptics	11	7,7
	Other**	11	7,7
	NSAIDs	10	7,0
	Biphosphonates	1	0,7

*Percentages have been calculated over the total number of patients of efficacy population (N=143). Patients can receive more than one treatment.

**Other pain treatments are listed in table 29.

Table 27: Other pain treatment at visit 1

		N	%*
Other pain treatment	**Metamizol**	6	4,2
	Anesthetic (Versatis)	2	1,4
	Anesthetic	1	0,7
	Hypnotic	1	0,7
	Nefopam (analgesics)	1	0,7

*Percentages have been calculated over the total number of patients of efficacy population (N=143). Patients can receive more than one treatment.

Visit 2 (week 2)

Table 28: Opioid treatment modified at visit 2

		N*	%
Treatment modify	**No**	109	77,9
	Yes	31	22,1
	Total	140	100,0

*3 missing data. Patients 33140712, 33140713 and 33140338.

Table 29: Opioid treatment changes at visit 2

		N	%
Opioid treatment changes	**Dose increase**	20	64,5
	Change opioid	8	25,8
	Dose reduction	3	9,7
	Total	31	100,0

Table 30: New opioid treatment at visit 2

		N	%
New opioid treatment at visit 2	**Oxycodonne**	3	37,5
	Buprenorphine	2	25,0
	Morphine	1	12,5
	Fentanyl	1	12,5
	Other*	1	12,5
	Total	8	100,0

*Patient 33140826: Methadone.

Table 31: Other paint treatment at visit 2

		N	%
Other pain treatment at visit 2	**Yes**	84	60,0
	No	56	40,0
	Total	140	100,0

*3 missing data. Patients 33140712, 33140713 and 33140338.

Table 32: Other pain treatment at visit 2

		N	%
Other pain treatment at visit 2	**Anti-Convulsants**	16	19,0
	Paracetamol	14	16,7
	Antidepressants+Anti-Convulsants	14	16,7
	Antidepressants	6	7,1
	Corticoids+Anti-Convulsants	5	6,0
	Neuroleptics+Paracetamol	3	3,6
	Antidepressants+Paracetamol	3	3,6
	Paracetamol+ NSAIDs	2	2,4
	Neuroleptics	2	2,4
	Antidepressants+NSAIDs	2	2,4
	Paracetamol+Anti-Convulsants	1	1,2
	Other (metamizol)	1	1,2
	NSAIDs	1	1,2
	Neuroleptics+Paracetamol+Other (AINES)	1	1,2
	Neuroleptics+Antidepressants+Paracetamol+ NSAIDs +Anti-Convulsants	1	1,2
	Neuroleptics+Anti-Convulsants	1	1,2
	Corticoids+Paracetamol+Other (benzodiazepines)	1	1,2
	Corticoids+Paracetamol+Anti-Convulsants	1	1,2
	Corticoids+Paracetamol	1	1,2
	Corticoids+Antidepressants+Anti-Convulsants	1	1,2
	Corticoids+Neuroleptics+Paracetamol+Anti-Convulsants+Other (metamizol)	1	1,2
	Corticoids	1	1,2
	Biphosphonates	1	1,2
	Antidepressants+Paracetamol+Anti-Convulsants	1	1,2
	Antidepressants+Other (anesthesic)	1	1,2
	Antidepressants+ NSAIDs +Anti-Convulsants+Other (ketamine)	1	1,2
	Anti-Convulsants+Other (anesthetic, capsaicine)	1	1,2
	Total	84	100,0

Table 33: Number of patient by pain treatment at visit 2

		N	%*
Other pain treatment	**Anti-convulsants**	44	31,4
	Antidepressants	30	21,4
	Paracetamol	30	21,4
	Corticoids	11	7,9
	Neuroleptics	9	6,4
	NSAIDs	7	5,0
	Other**	7	5,0
	Biphosphonates	1	0,7

*Percentages have been calculated over the total number of patients of efficacy population with visit 2 available (N=140). Patients can receive more than one treatment.
**Other pain treatments are listed in table 36.

Table 34: Other pain treatment at visit 2

		N	%*
Other pain treatmeent	**Metamizol**	2	1,4
	Anesthetic, capsaicine	1	0,7
	AINES	1	0,7
	Anesthetic	1	0,7
	Benzodiacepines	1	0,7
	Ketamine	1	0,7

*Percentages have been calculated over the total number of patients of efficacy population with visit 2 available (N=140). Patients can receive more than one treatment.

Visit 3 (week 4)

Table 35: Opioid treatment modify at visit 3

		N	%
Treatment modify	**No**	96	81,4
	Yes	22	18,6
	Total	118	100,0

**Patient 33140237: not available data.*

Table 36: Opioid treatment changes at visit 3

		N	%
Opioid treatment changes	**Dose increase**	14	63,6
	Change opioid	4	18,2
	Dose reduction	4	18,2
	Total	22	100,0

Table 37: New opioid treatment at visit 3

		N	%
New opioid treatment at visit 3	**Morphine**	2	50,0
	Fentanyl	1	25,0
	Other*	1	25,0
	Total	4	100,0

* Patient 33140686: Fentanyl, Morphin, Effentora.

Table 38: Other pain treatment at visit 3

		N	%
Other pain treatment at visit 2	**Yes**	73	61,3
	No	46	38,7
	Total	119	100,0

Table 39: Other pain treatment at visit 3

	N	%
Paracetamol	12	16,4
Antidepressants+Anti-convulsants	12	16,4
Corticoids+Anti-convulsants	7	9,6
Antidepressants	7	9,6
Anti-convulsants	6	8,2
Other*	3	4,1
Paracetamol+NSAIDs	2	2,7
Neuroleptics	2	2,7
Corticoids+Paracetamol+Anti-convulsants	2	2,7
Corticoids+Paracetamol	2	2,7
Corticoids+Antidepressants+Anti-convulsants	2	2,7
Antidepressants+Other **	2	2,7
Antidepressants+Anti-convulsants+Other ***	2	2,7
Paracetamol+Anti-convulsants	1	1,4
NSAIDs	1	1,4
Neuroleptics+Paracetamol+NSAIDs	1	1,4
Neuroleptics+Paracetamol	1	1,4
Neuroleptics+Anti-convulsants	1	1,4
Corticoids+Paracetamol+NSAIDs	1	1,4
Corticoids+Neuroleptics+Paracetamol+Anti-convulsants+Other (metamizole)	1	1,4
Corticoids+Neuroleptics+Paracetamol	1	1,4
Corticoids+Neuroleptics+Antidepressants+Anti-convulsants+Other (PPI, Tavor)	1	1,4
Corticoids+Antidepressants+Paracetamol	1	1,4
Corticoids+Antidepressants+NSAIDs	1	1,4
Antidepressants+Paracetamol	1	1,4
Total	73	100,0

*Other pain treatment: 2 metamizol and 1 auriculotherapy.
**Antidepresant + Other (local anesthetic); Antidepresant + Other (Antiepileptic).
***Antidepressants + Anti-convulsants + Other (Anesthesic); Antidepressants + Anti-convulsants + Other (Ketamine).

Table 40: Number of patient by pain treatment at visit 3

		N	%*
Other pain treatment	**Anti-convulsants**	35	29,7
	Antidepressants	29	24,6
	Paracetamol	26	22,0
	Corticoids	19	16,1
	Other**	9	7,6
	Neuroleptics	8	6,8
	NSAIDs	6	5,1

*Percentages have been calculated over the total number of patients of efficacy population with visit 3 available (N=118). Patient scan receive more than one treatment.
**Other pain treatments are listed in table 44.

Table 41: Other pain treatment at visit 3

		N	%*
Other pain treatment	**Metamizol**	3	2,5
	Anesthesic	1	,8
	Antiepileptic	1	,8
	Auriculotherapy	1	,8
	Ketamine	1	,8
	Local anesthetic	1	,8
	PPI, Tavor	1	,8

*Percentages have been calculated over the total number of patients of efficacy population with visit 3 available (N=118). Patients can receive more than one treatment.

5.5. Opioid Induced Constipation

The time from OIC diagnosis is defined as the elapsed time, in days, between the OIC diagnosis date and the informed consent date.

Table 42: Time from OIC diagnosis (month)

	N*	Mean	Q1	Media (Q2)	Q3	Standard deviation	Minumum	Maximum
Time from OIC diagnosis	111	1,5	,0	,2	1,2	4,3	,0	35,9

*There are 31 patients with unknown OIC diagnosis date. All patients have a confirmed diagnosis of OIC (monitoring data).
*Patient 33139733 indicated a wrong date so it has not been considered in this analysis.

Table 43: Straining during study

		Visit 1		Visit 2		Visit 3	
		N*	%	N**	%	N***	%
Straining	**Not at all**	14	10,4	20	15,2	22	20,0
	A little bit	25	18,5	33	25,0	31	28,2
	A moderate amount	29	21,5	46	34,8	35	31,8
	A great deal	53	39,3	30	22,7	18	16,4
	An extreme amount	14	10,4	3	2,3	4	3,6
	Total	135	100,0	132	100,0	110	100,0

*8 missing data (33139654, 33139958, 33139981, 33140223, 33140224, 33140319, 33140622 and 33140773).
**11 missing data (33139654, 33139762, 33139981, 33140179, 33140338, 33140622, 33140676, 33140712, 33140713, 33140751 and 33140818).
***There are 9 missing data (33139762, 33139981, 33140179, 33140338, 33140676, 33140712, 33140713 and 33140818).

Note: there are 24 patients that have not completed visit 3.

Table 44: Sensation of incomplete evacuation during study

		Visit 1		Visit 2		Visit 3	
		N*	%	N**	%	N***	%
Sensation of incomplete evacuation	**Yes**	109	79,6	80	60,6	63	55,6
	No	28	20,4	52	39,4	50	44,2
	Total	137	100,0	132	100,0	113	100,0

*6 missing data (33139958, 33140453, 33140622, 33140751, 33139745 and 33140319).
**11 missing data (33139762, 33139981, 33140179, 33140338, 33140622, 33140676, 33140712, 33140713, 33140751, 33140818 and 33141048).
***There are 6 missing data (33140712, 33140713, 33140818, 33141048, 33140237 and 33141127)

Note: there are 24 patients that have not completed visit 3.

Table 45: BSS during study

		Visit 1		Visit 2		Visit 3	
		N	%	N*	%	N**	%
BSS-Stool consistency	**1**	48	33,6	25	18,5	22	18,8
	2	24	16,8	24	17,8	25	21,4
	3	19	13,3	22	16,3	16	13,7
	4	13	9,1	26	19,3	23	19,7
	5	11	7,7	16	11,9	8	6,8
	6	3	2,1	12	8,9	8	6,8
	7	9	6,3	5	3,7	6	5,1
	Not available	16	11,2	5	3,7	9	7,7
	Total	143	100,0	135	100,0	117	100,0

*8 missing data (33139762, 33140179, 33140338, 33140622, 33140712, 33140713, 33140751 and 33140818).
**There are 2 missing data (33141127 and 33140237).

Note: there are 24 patients that have not completed visit 3.

Table 46: Previous laxative treatments (Yes/No) at visit 1

		Visit 1	
		N	%
Previous laxative treatments	**Yes**	104	72,7
	No	39	27,3
	Total	143	100,0

Table 47: Other laxative treatments (Yes/No) during the study

		Visit 2		Visit 3	
		N*	%	N**	%
Other laxative treatments	**Yes**	105	75,0	43	36,4
	No	35	25,0	75	63,6
	Total	140	100,0	118	100,0

*3 missing data (33140338, 33140712 and 33140713).
**There are 1 missing data (33141127).

Note: there are 24 patients that have not completed visit 3.

Table 48: Previous laxative treatments at visit 1

		Visit 1*	
		N	%
Laxative treatment	**Osmotic**	83	79,8
	Stimulant	32	30,8
	Other****	19	18,3
	Stool softeners	12	11,5
	Bulking agents	4	3,8
	Linaclotide	1	1,0

*Percentages have been calculated over the total number of patients with previous laxative treatment (N=104). Patients can receive more than one laxative treatment.

Table 49: Other laxative treatments during study

		Visit 2**		Visit 3***	
		N	%	N	%
Laxative treatment	**Osmotic**	24	68,6	27	62,8
	Stimulant	8	22,9	12	27,9
	Other****	10	28,6	6	14,0
	Stool softeners	2	5,7	10	23,3
	Bulking agents	1	2,9	1	2,3
	Linaclotide	0	,0	0	,0

**Percentages have been calculated over the total number of patients with concomitant laxative treatment at visit 2 (N=35). Patients can receive more than one laxative treatment.
*Percentages have been calculated over the total number of patients with concomitant laxative treatment at visit 3 (N=43). Patients can receive more than one laxative treatment.
****Other pain treatments are listed in table 50 (visit 1), 51 (visit 2) and 52 (visit 3).

Note: there are 24 patients that have not completed visit 3.

Table 50: Other laxative treatments at visit 1

		N	%*
Other laxative treatments at visit 1	**Enema**	10	9,6
	Glycerin suppository	2	1,9
	Lubricant	1	1,0
	Enema + Sennoides	1	1,0
	Micralax, lactulose and glicerin suppositories	1	1,0
	Natural laxative	1	1,0
	Rectal lavement	1	1,0
	Senna	1	1,0
	Stimulating the body's defecation reflex	1	1,0

*Percentages have been calculated over the total number of patients with previous laxative treatment (N=104). Patients can receive more than one laxative treatment.

Table 51: Other laxative treatments at visit 2

		N	%*
Other laxative treatments at visit 2	**Enema**	4	11,4
	Senna	2	5,7
	Duphalac	1	2,9
	Micralax	1	2,9
	Natural laxative	1	2,9
	Patient took a cleaning enema 4 times from last visit	1	2,9

*Percentages have been calculated over the total number of patients with concomitant laxative treatment at visit 2(N=35). Patients can receive more than one laxative treatment.

Table 52: Other laxative treatments at visit 3

		N	%*
Other laxative treatments at visit 3	**Enema**	2	4,7
	Natural laxative	1	2,3
	Senna	1	2,3
	Suppository	1	2,3
	Unknown	1	2,3

*Percentages have been calculated over the total number of patients with concomitant laxative treatment at visit 3 (N=43). Patients can receive more than one laxative treatment.

Table 53: Average pain at visit 1

	N*	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Pain average at visit 1	131	4,4	2,0	4,0	7,0	2,8	,0	10,0

*12 missing data (33139745, 33140107, 33140130, 33140223, 33140224, 33140319, 33140453, 33140622, 33140751, 33140773, 33140818 and 33140826).

Table 54: Worst pain at visit 1

	N*	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Pain worst at visit 1	131	5,9	4,0	6,0	8,0	3,2	,0	10,0

*12 missing data (33139745, 33140107, 33140130, 33140223, 33140224, 33140319, 33140453, 33140622, 33140751, 33140773, 33140818 and 33140826).

6. TREATMENT DESCRIPTION

6.1. Treatment administration; general considerations.

Treatment description has been performed for efficacy population.

6.2. Naloxegol treatment description.

Time from OIC diagnosis to naloxegol is defined as the time, in months, between the OIC diagnosis date and the naloxegol treatment start date.

Table 55: Time from OIC diagnosis to naloxegol (months)

	N	Mean	Q1	Median	Q3	Standard deviation	Minimum	Maximum
Time from OIC diagnosis to naloxegol	111	1,6	,0	,2	1,2	4,3	,0	35,9

*There are 31 patients with unknown OIC diagnosis date. All patients have a confirmed diagnosis of OIC (monitoring data).
*Patient 33139733 indicated a wrong date so he has not been considered in this analysis.

Naloxegol treatment time is defined as the time, in days, between the treatment start date and the study completion 4 weeks observation, death, subject withdrawn whichever occurs first. In the rest of the subjects, the last follow-up has been taken.

Table 56: Naloxegol treatment time (days)

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minimum	Maximum
Time of treatment with naloxegol (month)	143	27,9	26,0	28,0	30,0	10,9	1,0	104,0

Table 57: Initial naloxegol dose (mg)

	N	Mean	Q1	Median (Q2)	Q3	Standar deviation	Minimum	Maximum
Initial dose of naloxegol (mg)	143	22,8	25,0	25,0	25,0	5,4	12,5	50,0

Table 58: Initial naloxegol dose (mg) II

		N	%
Initial dose of naloxegol (mg)	**25,0**	115	80,4
	12,5	27	18,9
	50,0	1	,7
	Total	143	100,0

Treatment modification at visit 2

Table 59: Naloxegol interruption at visit 2

		N	%
Treatment interruption at visit 2	**No**	126	90,0
	Yes	14	10,0
	Total	140	100,0

*3 missing data (33140712, 33140338 and 33140713).

Table 60: Naloxegol interruption number of days at visit 2

		N	%
Interruption No. days	**1**	4	28,6
	2	2	14,3
	3	2	14,3
	4	2	14,3
	5	1	7,1
	6	1	7,1
	13	1	7,1
	17	1	7,1
	Total	14	100,0

Note: Visit dates were modified with respect to the intervals foreseen in the protocol due to the Christmas holidays.

Table 61: Naloxegol adjustment at visit 2

		N	%
Treatment adjustment at visit 2	**No**	136	95,1
	Yes	4	2,8
	Total	140	100,0

*3 missing data (33140712, 33140338 and 33140713).

Table 62: Naloxegol adjustment by patient at visit 2

StudySubjectID	Change (visit 1- visit 2)	Dose at visit 1 (initial dose)	Dose at visit 2
33140767	Dose increased	25,0	50
33140787	Dose increased	25,0	50
33140135	Dose increased	12,5	25
33140831	Dose increased	12,5	25

Treatment modification at visit 3

Table 63: Naloxegol interruption at visit 3

		N	%
Treatment interruption at visit 3	**No**	107	75,9
	Yes	11	7,8
	Total	118	100,0

Table 64: Naloxegol interruption number of days at visit 3

		N	%
Interruption No. Days at visit 3	**1**	3	30,0
	4	1	10,0
	7	2	20,0
	10	2	20,0
	13	1	10,0
	15	1	10,0
	Total	10	100,0

*1 missing data (33140338).

Table 65: Naloxegol adjustment at visit 3

		N	%
Treatment adjustment at visit 3	**No**	112	79,4
	Yes	6	4,3
	Total	118	100,0

Table 66: Naloxegol adjustment by patient at visit 3

StudySubjectID	Change (visit 2- visit 3)	Dose at visit 1* (mg)	Dose at visit 3 (mg)	Dose at visit 3 (mg) (change number 2)
33140469	Dose increased	25,0	50,0	-
33140227	Dose increased-Dose reduction	25,0	50,0	25,0
33140142	Dose increased	25,0	50,0	-
33141083	Dose increased	25,0	50,0	-
33140283	Dose increased	12,5	25,0	-
33140316	Dose increased	12,5	25,0	-

*These patients do not change the dose of naloxegol at visit 2.

6.3. Other concomitant laxative treatments

This analysis has been included at section "5.5 Opioid induced constipation".

7. PATIENTS DIARY

The information registered on patients diary has beem analyzed for the efficacy population.

Bowel movements per week:

- Bowel movement at week 1 is defined as the sum of bowel movements on days 1 to 7.
- Bowel movement at week 2 is defined as the sum of bowel movements on days 8 to 14.
- Bowel movement at week 3 is defined as the sum of bowel movements on days 15 to 21
- Bowel movement at week 4 is defined as the sum of bowel movements on days 22 to 30.

Table 67: Total number of bowel movements per week

		N	%
Bowel movements at week 1 per patient	**1**	4	3,9
	2	12	11,8
	3	11	10,8
	4	19	18,6
	5	12	11,8
	6	18	17,6
	7	26	25,5
	Total	102	100,0
Bowel movements at week 2 per patient	**1**	4	4,2
	2	13	13,7
	3	13	13,7
	4	8	8,4
	5	20	21,1
	6	14	14,7
	7	23	24,2
	Total	95	100,0
Bowel movements at week 3 per patient	**1**	4	4,5
	2	11	12,5
	3	14	15,9
	4	10	11,4
	5	17	19,3
	6	11	12,5
	7	21	23,9
	Total	88	100,0
Bowel movements at week 4 per patient	**1**	5	5,9
	2	7	8,2
	3	12	14,1
	4	16	18,8
	5	10	11,8
	6	16	18,8

7	17	20,0
8	2	2,4
Total	85	100,0

Laxative used per week:

Note: The following 24 patients have indicated naloxegol as laxative treatment used: 33139637, 33139701, 33139916, 33139958, 33140088, 33140127, 33140135, 33140142, 33140184, 33140213, 33140227, 33140242, 33140312, 33140517, 33140625, 33140703, 33140739, 33140751, 33140760, 33140767, 33140787, 33140826, 33140847 and 33141083.

This information has been monitored and all these patients have used naloxegol as study treatment not as rescue treatment and those. These patients have not been considered to have used rescue laxative treatment.

Table 68: Number of total laxative uses per week

		N	%
Laxative week 1 (N=102)	**Bulking Agents**	**68**	66,7
	Osmotic Laxatives	**19**	18,6
	Stimulant Laxatives	**19**	18,6
	Stool Softeners	**9**	8,8
	Bulking Agents + Stimulant Laxatives	**5**	4,9
	Osmotic Laxatives + Stool Softeners	**5**	4,9
	Stimulant Laxatives + Stool Softeners	**5**	4,9
	Not available	**3**	2,9
	Bulking Agents + Stool Softeners	**2**	2,0
	Osmotic Laxatives + Stimulant Laxatives	**2**	2,0
	Bulking Agents + Osmotic laxatives	**1**	1,0
	Bulking Agents + Osmotic laxatives + Stool Softeners	**1**	1,0
	Osmotic Laxatives + Stimulant Laxatives + Bulking Agents	**1**	1,0
	Stool Softeners + Stimulant Laxatives	**1**	1,0
Laxative week 2 (N=95)	**Stool Softeners**	**38**	40,0
	Osmotic Laxatives	**30**	31,6
	Bulking Agents	**19**	20,0
	Stimulant Laxatives	**19**	20,0
	Bulking Agents + Stimulant Laxatives	**10**	10,5
	Others	**4**	4,2
	Not available	**3**	3,2
	Bulking Agents + Osmotic Laxatives	**1**	1,1
	Bulkiung Agents + Stimulant Laxatives+ Stool Softeners	**1**	1,1
	Bulkiung Agents + Stool Softeners	**1**	1,1
	Osmotic Agents + Stool Softeners	**1**	1,1
	Osmotic Laxative + Stool Softeners	**1**	1,1
	Stimulant Laxatives + Stool Softeners	**1**	1,1
	Stool Softeners + Osmotic Laxative	**1**	1,1
Laxative week 3 (N=88)	**Bulking Agents**	**58**	65,9
	Osmotic Laxative	**15**	17,0
	Osmotic Laxatives	**14**	15,9
	Stimulant Laxatives	**10**	11,4
	Bulking Agents + Stool Softeners	**10**	11,4
	Stool Softeners	**7**	8,0
	Not Available	**5**	5,7
	Bulking Agents + Stimulant Laxatives	**3**	3,4
	Bulkiung Agents + Stimulant Laxatives + Stool Softeners	**1**	1,1
	Osmotic Laxative + Stimulant laxatives + Bulking Agents	**1**	1,1
	Osmotic Laxatives + Stool Softeners	**1**	1,1
	Others	**1**	1,1
Laxative week 4 (N=85)	**Bulking Agents**	**56**	65,9
	Osmotic Laxatives	**25**	29,4

		N	%
	Stimulant Laxatives	**21**	24,7
	Not available	**12**	14,1
	Bulking Agents + Stimulant Laxatives	**3**	3,5
	Stool Softeners	**2**	2,4
	Bulking Agents + Others	**1**	1,2
	Bulking Agents + Stool Softeners	**1**	1,2
	Others	**1**	1,2
	Stimulant Laxatives + Stool Softeners	**1**	1,2

*Percentajes calculated over total of patient with information in each week. Week 1 N=102, week 2 N=96, week 3 N= 88 and week 4 N=85.

Table 69: Average of pain level per week

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Average of pain at week 1	117	3,0	,9	2,7	4,7	2,4	,0	8,3
Average of pain at week 2	105	2,7	,9	2,0	4,0	2,4	,0	8,1
Average of pain at week 3	95	2,7	,7	2,4	4,0	2,3	,0	8,1
Average of pain at week 4	90	2,3	,4	1,9	3,4	2,3	,0	9,4

Table 70: Worst pain level per week

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Worst pain level at week 1	99	4,2	1,3	4,4	7,0	3,0	,0	9,4
Worst pain level at week 2	95	3,7	1,1	3,3	6,1	2,8	,0	9,9
Worst pain level at week 3	85	3,7	1,1	3,9	5,7	2,6	,0	8,9
Worst pain level at week 4	80	3,7	1,3	3,3	5,9	2,9	,0	10,9

8. STUDY ENDPOINTS

8.1. Efficacy Assessment; general considerations

The efficacy analysis set has been the efficacy population, defined as all patients who meet all selection criteria, received at least 1 dose of study drug and have at least one post-baseline efficacy assessment.

8.2. Primary saffety endpoint

The primary saffety end point is the incidence of adverse events leading to study discontinuation.

- Disontinuation of study due to adverse events related to naloxegol treatment.

Table 71: Discontinuation related with naloxegol reaction

		Discontinuation reason
1	**33139577**	Naloxegol Adverse Reaction: Abdominal pain (patient in treatment with metadona). Grade: Moderate
2	**33139762**	Naloxegol Adverse Reaction: abdominal pain and nausea. Grade: Moderate
3	**33139981**	Naloxegol Adverse Reaction: Diarrhea. Grade UNK
4	**33140105**	Naloxegol Adverse Reaction: Intestinal perforation. Grade: Severe
5	**33140185**	Naloxegol Adverse Reaction: abdominal pain. Grade: Moderate
6	**33140186**	Naloxegol Adverse Reaction: abdominal pain. Grade: Moderate
7	**33140190**	Naloxegol Adverse Reaction: abdominal pain. Grade: Moderate
8	**33140306**	Naloxegol Adverse Reaction: Abdominal cramps. Grade: Unknown
9	**33140458**	Naloxegol Adverse Reaction: fatigue. Grade: Moderate
10	**33140567**	Naloxegol Adverse Reaction: diarrhea. Grade: Moderate
11	**33140760**	Naloxegol Adverse Reaction: Severe abdominal cramps. Grade: Moderate
12	**33139734**	Naloxegol Adverse Reaction: abdominal colic. Grade: Mild

12 of the 170 patients (7.1%) indicated that the study discontinuation was due to adverse events is related to naloxegol.

In addition to the naloxegol-related interruptions, there are two patients who iscontinue treatment by decision of the investigator. In both cases, loss of efficacy has been indicated.

- Patient 33139931: Efficacy loss
- Patient 33140135: Low efficacy (no defecation under 25 mg naloxegol)

8.3. Primary efficacy endpoint

The primary efficacy end point is response rate during the 4 weeks treatment period. Response is defined as three or more bowel movements (without the use of rescue laxative treatment in the previous 24 hours) per week.

It is considered response if patients have response in 3 of 4 weeks of study, according to the previous definition.

Population 1

Patients with 4 weeks of treatment and 28 days of the diary.

Table 72: Response over population 1

		N	%
Response	**Yes**	55	72,4
	No	21	27.6
	Total	76	100,0

72,4% of patients responded treatment (N=55). CI 95%: 62,3%; 82,4%.

Table 73: Average number of bowel movements per week over population 1

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Average number of bowel movements per week	76	6,9	4,5	6,0	8,8	3,5	2	18,5

The average number of bowel movements per week in population 1 is 6,9 (N=76). CI 95%: 6,113; 7,687.

Table 74: Average number of bowel movements per week over population 1 (only patients with response)

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Average number of bowel movements per week	55	8,1	5,8	7,5	9,5	3,0	18,5	3,3

The average number of bowel movements per week over patients that have responded in population 1 is 8,1 (N=55). CI 95%: 7,306; 8,894.

Population 2

Patient from the efficacy population with at least 21 days of the diary.

Table 75: Response over population 2

		N	%
Response	**Yes**	74	75,5
	No	24	24,5
	Total	98	100,0

75,5% of patients responded treatment (N=74). CI 95%: 67,0%; 84,0%.

Table 76: Average number of bowel movements at week over population 2

	N	Mean	Q1	Mediana (Q2)	Q3	Standard deviation	Minumum	Maximum
Average number of bowel movements per week	98	6,6	4,5	5,9	8,3	3,2	2,0	18,5

The average number of bowel movements per week in population 2 is 6,6 (N=98). CI 95%: 5,966; 7,233.

Table 77: Average number of bowel movements at week over population 2 (only patients with response)

	N	Mean	Q1	Median (Q2)	Q3	Standard deviation	Minumum	Maximum
Average number of bowel movements per week	74	7,6	5,5	7,0	8,8	3,0	18,5	3,1

The average number of bowel movements per week over patients that have responded in population 2 is 7,6 (N=74). CI 95%: 6,916; 8,284.

8.4. Secondary efficacy end points

- Proportion of patients that have a BFI score change of ≥12 points at the end of the study treatment (4 weeks).
- Proportion of patients that have a BFI score <30 at the end of the study (patients adequately treated).

Bowel Function Index

1. How would you rate the ease of defecation during the last 7 days according to patient assessment? (0 = Easy / No difficulty - 100 = Severe difficulty)
2. Does your patient feel that his/her bowel evacuation has been incomplete during the last 7 days? (0 = Not at all - 100 = Very strongly)
3. How would you judge your patient's constipation throughout the last 7 days? (0 = No constipation at all - 100 = Very heavily constipated)

Total: Average of three items.

Table 78: BFI score change ≥12 points at the end of the study treatment

		N*	%
BFI score change ≥12 points	**No**	42	35,9
	Yes	75	64,1
	Total	117	100,0

*Total BFI score not available in week 4 for 26 patients.

Table 79: BFI score <30 at the end of the study treatment

		N*	%
Patients adequately treated	**No**	74	63,2
	Yes	43	36,8
	Total	117	100,0

*Total BFI score not available in week 4 for 26 patients.

Table 80: BFI Score: Screening visit

	N	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
BFI question 1	143	68,9	23,5	50,0	70,0	85,0	,0	100,0
BFI question 2	143	66,2	28,6	50,0	70,0	90,0	,0	100,0
BFI question 3	143	71,0	25,1	60,0	80,0	90,0	,0	100,0
BFI total score	143	68,7	20,4	56,7	70,0	83,3	6,7	100,0

Table 81: BFI Score: Week 2

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
BFI question 1	136	49,7	26,9	30,0	50,0	70,0	,0	100,0
BFI question 2	136	49,9	27,3	30,0	50,0	70,0	,0	100,0
BFI question 3	136	47,3	28,9	25,0	50,0	70,0	,0	100,0
BFI total score	136	49,0	25,2	30,0	50,0	65,8	,0	100,0

*Not available information in visit week 2 for 7 patients.

Table 82: BFI Score: Week 4

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
BFI question 1	117**	40,5	27,1	20,0	40,0	60,0	,0	90,0
BFI question 2	118	43,0	28,4	20,0	41,5	60,0	,0	100,0
BFI question 3	118	39,7	29,7	10,0	40,0	65,0	,0	100,0
BFI total score	117**	41,1	26,5	20,0	41,7	60,0	,0	96,7

*Not available information in visit week 4 for 25 patients.
**Patient 33140767 has no information in week 4 question 1.

Table 83: BFI Score: Screening visit (V1) vs week 2 visit (V2)

	Paired differences							
				95% confidence interval of the difference				
	Mean	Standard deviation	Deviation average error	Lower	Upper	t	gl	Sig. (bilateral)
BFI question 1 V1 - BFI question 1 V2	18,022	30,070	2,588	12,904	23,141	6,964	134	**,000**
BFI question 2 V1 - BFI question 2 V2	15,733	30,894	2,659	10,474	20,992	5,917	134	**,000**
BFI question 3 V1 - BFI question 3 V2	23,741	35,179	3,028	17,752	29,729	7,841	134	**,000**
BFI total score V1 - BFI total score V2	19,16543	27,40386	2,35855	14,50063	23,83023	8,126	134	**,000**

Table 84: BFI Score: Screening visit (V1) vs week 4 visit (V3)

	Paired differences							
				95% confidence interval of the difference				
	Mean	Standard deviation	Deviation average error	Lower	Upper	t	gl	Sig. (bilateral)
BFI question 1 V1 - BFI question 1 V3	28,043	32,344	3,003	22,095	33,992	9,338	115	**,000**
BFI question 2 V1 - BFI question 2 V3	23,889	37,104	3,430	17,095	30,683	6,964	116	**,000**
BFI question 3 V1 - BFI question 3 V3	31,838	34,887	3,225	25,450	38,226	9,871	116	**,000**
BFI total score V1 - BFI total score V3	28,05460	31,55772	2,93006	22,25071	33,85848	9,575	115	**,000**

- Change in stool consistency (Bristol stool scale).

The mean daily Bristol stool scale (BSS) score for an interval has been calculated as the sum of daily values for the interval divided by the number of days in which the data were collected. For week 2 BSS Score, all bowel movements indicated in patient's diary with visit day at much 14 days have been considered. For week 4 BSS Score, all bowel movements indicated in patient's diary have been considered. Days in which data has been collected for week 2 BSS Score have been considered all days with visit day at much 14 days in which data where collected.

Change from baseline in the mean BSS score has been calculated for weeks 2 and 4 as the post-baseline value minus the baseline value, where baseline is the mean daily BSS score recorded during the baseline visit. Positive changes from baseline indicate improvement.

Table 85: BSS Score: Difference between screening visit and week 2

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Difference between screening visit and week 2	112	,8	1,8	-,2	,8	2,2	-3,0	5,1

*Not available information in patient's diary for 14 patients but information available in screening visit.
No bowel movements for 1 patient.
Uknown is indicated in screening visit BSS Score for 5 patients.
Not available is indicated in screening visit BSS Score for 8 patients.
Not available information in patient's diary and Not available is indicated in screening visit BSS Score for 2 patients.
Not available information in patient's diary and Unknown is indicated in screening visit BSS Score for 1 patient.

Table 86: BSS Score: Difference between screening visit and week 4

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Difference between screening visit and week 4	111	,9	1,8	-,1	,8	2,0	-3,2	5,0

*Not available information in patient's diary for 15 patients but information available in screening visit.
No bowel movements for 1 patient.
Uknown is indicated in screening visit BSS Score for 5 patients.
Not available is indicated in screening visit BSS Score for 8 patients.
Not available information in patient's diary and Not available is indicated in screening visit BSS Score for 2 patients.
Not available information in patient's diary and Unknown is indicated in screening visit BSS Score for 1 patient.

- Time to first post-dose bowel movement

The time to first post-dose bowel movement is defined as the time from the first administration of naloxegol to the first bowel movement registered in patient diary.

Table 87: Time to first post-dose bowel movement (days)

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Time to first post-dose bowel movement	125	1,9	1,7	1,0	1,0	2,0	1,0	14,0

*Not available information in patient's diary for 25 patients.

*No bowel movement for patient 33141127.

- Change in Patient Assessment of Constipation – Quality of Life Questionnaire (PAC-QOL).

PAC-QOL

For the PAC-QOL, each of the 28 items is scored from 0 to 4. For items 18, 25, 26, 27, and 28, higher scores represent better outcomes. The scores for these items have been reversed (reversed score=4-original score), so that higher scores represent worse outcomes for all items. The 28-item PAC-QOL is divided into 4 subscales:

- Physical discomfort (items 1 to 4)
- Psychosocial discomfort (items 5 to 12)
- Worries/concerns (items 13 to 23)
- Satisfaction (items 24 to 28).

Table 88: PAC-QOL: Screening visit

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Physical discomfort	139	2,1	0,9	1,5	2,3	2,8	0,0	4,0
Pshychosocial discomfort	136	1,5	1,0	0,7	1,5	2,2	0,0	3,6
Worries/Concerns	138	1,9	0,8	1,4	2,0	2,6	0,1	3,9
Satisfaction	135	2,3	0,7	2,0	2,4	3,0	0,4	3,2
Total score	132	1,9	0,7	1,5	1,9	2,4	0,3	3,4

*Physical discomfort subscale not available for 4 patients.
Pshychosocial discomfort subscale not available for 7 patients.
Worries/Concerns subscale not available for 5 patients.
Satisfaction subscale not available for 8 patients.
PAC-QOL scale not available for 11 patients.

Table 89: PAC-QOL: Visit week 2

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Physical discomfort	131	1,5	0,9	0,8	1,5	2,0	0,0	4,0
Pshychosocial discomfort	128	0,9	0,8	0,3	0,8	1,4	0,0	3,6
Worries/Concerns	129	1,3	0,8	0,7	1,3	1,9	-0,1	3,8
Satisfaction	129	1,5	1,0	0,6	1,4	2,2	-0,8	3,2
Total score	125	1,3	0,7	0,7	1,3	1,7	-0,2	3,4

*Physical discomfort subscale not available for 1 patient.
Pshychosocial discomfort subscale not available for 4 patients.
Worries/Concerns subscale not available for 3 patients.
Satisfaction subscale not available for 3 patients.
PAC-QOL scale not available for 7 patients.

Table 90: PAC-QOL: Visit week 4

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Physical discomfort	115	1,2	0,9	0,5	1,0	1,8	0,0	4,0
Pshychosocial discomfort	113	0,7	0,7	0,1	0,5	1,1	0,0	3,6
Worries/Concerns	114	1,2	0,8	0,5	1,2	1,7	-0,1	2,9
Satisfaction	115	1,3	1,0	0,4	1,4	2,0	-0,8	3,2
Total score	112	1,1	0,7	0,6	0,9	1,6	-0,2	3,3

*Physical discomfort subscale not available for 4 patients.
Pshychosocial discomfort subscale not available for 6 patients.
Worries/Concerns subscale not available for 5 patients.
Satisfaction subscale not available for 4 patients.
PAC-QOL scale not available for 7 patients.

Change from baseline in the PAC-QOL subscale and total scores have been calculated for weeks 2 and 4 as the post-baseline value minus the baseline value, where baseline is the value collected into the baseline visit. Negative changes from baseline indicate improvement.

Table 91: PAC-QOL: Difference between screening visit and week 2

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Difference in Physical discomfort	128	-0,6	1,0	-1,3	-0,5	0,0	-2,8	1,8
Difference in Pshychosocial discomfort	124	-0,5	0,9	-1,0	-0,3	0,0	-2,9	1,8
Difference in Worries/Concerns	126	-0,5	0,8	-1,1	-0,5	0,0	-3,0	1,8
Difference in Satisfaction	124	-0,8	1,1	-1,8	-0,6	0,0	-3,4	2,2
Difference Total score	118	-0,6	0,7	-1,1	-0,5	0,0	-2,4	1,4

*Difference Physical discomfort subscale not available for 4 patients.
Difference Pshychosocial discomfort subscale not available for 8 patients.
Difference Worries/Concerns subscale not available for 6 patients.
Difference Satisfaction subscale not available for 8 patients.
Difference PAC-QOL scale not available for 14 patients.

Table 92: PAC-QOL: Difference between screening visit and week 2 II

	Paired differences							
				Difference confidence interval 95%				
	Mean	Standard deviation	Deviation mean error	Lower	Upper	t	gl	Sig. (bilateral)
Physical discomfort	0,62	0,95	0,08	0,46	0,79	7,396	127	**0,000**
Pshychosocial discomfort	0,51	0,85	0,08	0,36	0,66	6,696	123	**0,000**
Worries/Concerns	0,54	0,81	0,07	0,40	0,69	7,474	125	**0,000**
Satisfaction	0,84	1,13	0,10	0,64	1,04	8,286	123	**0,000**
Total score	0,61	0,74	0,07	0,48	0,75	9,002	117	**0,000**

Table 93: PAC-QOL: Difference between screening visit and week 4

	N*	Mean	Standard deviation	Q1	Median (Q2)	Q3	Minimum	Maximum
Difference in Physical discomfort	112	-0,9	1,0	-1,8	-0,8	0,0	-3,8	1,3
Difference in Pshychosocial discomfort	109	-0,7	0,9	-1,1	-0,6	0,0	-3,2	1,6
Difference in Worries/Concerns	110	-0,8	1,0	-1,4	-0,6	-0,1	-3,1	1,9
Difference in Satisfaction	109	-1,1	1,1	-1,8	-1,0	0,0	-3,4	1,6
Difference Total score	105	-0,9	0,8	-1,4	-0,8	-0,3	-2,7	1,1

*Difference Physical discomfort subscale not available for 7 patients.
Difference Pshychosocial discomfort subscale not available for 10 patients.
Difference Worries/Concerns subscale not available for 9 patients.
Difference Satisfaction subscale not available for 10 patients.
Difference PAC-QOL scale not available for 14 patients.

Table 94: PAC-QOL: Difference between screening visit and week 4 II

	Paired differences							
				Difference confidence interval 95%				
	Mean	Standard deviation	Deviation mean error	Lower	Upper	t	gl	Sig. (bilateral)
Physical discomfort	0,92	1,01	0,10	0,73	1,10	9,580	111	**0,000**
Pshychosocial discomfort	0,74	0,92	0,09	0,56	0,91	8,351	108	**0,000**
Worries/Concerns	0,79	0,97	0,09	0,60	0,97	8,457	109	**0,000**
Satisfaction	1,08	1,12	0,11	0,87	1,29	10,084	108	**0,000**
Total score	0,86	0,81	0,08	0,70	1,01	10,887	104	**0,000**

- Patient satisfaction (PGI-I).

To evaluate the global improvement, the Patient Global Impression of Improvement (PGI-I) has been used. Number and percentage of patients in each category of response in the scale has been provided. The categories have been graded according to de following criteria: 1. Very much better; 2. Much better; 3. A little better; 4. No change; 5. A little worse; 6. Much worse; 7. Very much worse.

Table 95: PGI-I

		N*	%
PGI-I	**Very much better**	15	12,7
	Much better	36	30,5
	A little better	38	32,2
	No change	22	18,6
	A little worse	3	2,5
	Much worse	3	2,5
	Very much worse	1	,8
	Total	118	100,0

*Data not available for patient 33140196.

9. SAFETY ASSESSMENT

9.1. Safety Assessment; general considerations

Analysis of adverse events has been performed for "safety population" (N=170), defined as all patients who meet all selection criteria and received at least 1 dose of study drug. Adverse events have been evaluated using NCI-CTC V4.03 criteria. The terms have been coded using MedDRA last version.

The adverse events indicated in the eCRF have been analyzed.

9.2. Adverse Events: general considerations

The analysis of adverse events has been provided per subject. The maximum of the degrees has been calculated for each adverse events collected throughout the study of each subject. The adverse events indicated in the eCRF have been analyzed.

9.2.1. Adverse Events

An adverse event is any undesired medical event that the patient could present during treatment with a drug, but which is not necessarily causally related to said drug.

Table 96: Patients with at least one adverse event

		N	%
At least one adverse event	**No**	81	47,6
	Yes	89	52,4
	Total	170	100,0

Table 97: Adverse events by grade

		Grade											
		1		2		3		4		5		Total	
SOC (System Organ Class)	**PT (Preferred Term)**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Blood and lymphatic system disorders	**Anaemia**	3	1,8	4	2,4	5	2,9	0	0,0	0	0,0	12	7,1
	Elephantiasis	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Febrile neutropenia	0	0,0	0	0,0	0	0,0	1	0,6	0	0,0	1	0,6
	Neutropenia	0	0,0	2	1,2	3	1,8	1	0,6	0	0,0	6	3,5
	Thrombocytopenia	1	0,6	1	0,6	0	0,0	1	0,6	0	0,0	3	1,8
	Total	4	2,4	7	4,1	9	5,3	3	1,8	0	0,0	23	13,5
Ear and labyrinth disorders	**Vertigo**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
Eye disorders	**Vision blurred**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Visual impairment	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Xerophthalmia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	3	1,8	0	0,0	0	0,0	0	0,0	0	0,0	3	1,8
Gastrointestinal disorders	**Abdominal distension**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Abdominal pain	6	3,5	7	4,1	4	2,4	0	0,0	0	0,0	17	10,0
	Abdominal pain lower	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Anal fissure	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Ascites	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Constipation	2	1,2	2	1,2	1	0,6	0	0,0	0	0,0	5	2,9
	Diarrhoea	3	1,8	5	2,9	1	0,6	0	0,0	0	0,0	9	5,3
	Duodenal obstruction	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Dysphagia	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Faeces hard	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Flatulence	0	0,0	2	1,2	1	0,6	0	0,0	0	0,0	3	1,8
	Gastroenteritis	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2
	Gastrointestinal motility disorder	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Gastrointestinal pain	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2
	Intestinal perforation	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6	1	0,6
	Nausea	8	4,7	6	3,5	1	0,6	0	0,0	0	0,0	15	8,8
	Oral pain	1	0,6	1	0,6	0	0,0	0	0,0	0	0,0	2	1,2
	Rectal haemorrhage	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2
	Vomiting	5	2,9	4	2,4	0	0,0	0	0,0	0	0,0	9	5,3
	Total	35	20,6	29	17,1	10	5,9	0	0,0	1	0,6	75	44,1
General disorders and administration site conditions	**Asthenia**	4	2,4	5	2,9	1	0,6	0	0,0	0	0,0	10	5,9
	Chest pain	0	0,0	1	0,6	1	0,6	0	0,0	0	0,0	2	1,2
	Chills	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Condition aggravated	0	0,0	0	0,0	0	0,0	1	0,6	0	0,0	1	0,6
	Decreased appetite	0	0,0	1	0,6	0	0,0	0	0,0	1	0,0	1	0,6
	Disease progression	1	0,6	0	0,0	1	0,6	0	0,0	14	8,2	16	9,4
	Fatigue	4	2,4	7	4,1	1	0,6	0	0,0	0	0,0	12	7,1

		Grade											
		1		2		3		4		5		Total	
SOC (System Organ Class)	PT (Preferred Term)	N	%	N	%	N	%	N	%	N	%	N	%
	General physical health deterioration	0	0,0	1	0,6	1	0,6	0	0,0	0	0,0	2	1,2
	Mucosal inflammation	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Oedema	2	1,2	1	0,6	0	0,0	0	0,0	0	0,0	3	1,8
	Oedema peripheral	3	1,8	1	0,6	0	0,0	0	0,0	0	0,0	4	2,4
	Pain	0	0,0	3	1,8	2	1,2	0	0,0	0	0,0	5	2,9
	Pyrexia	4	2,4	1	0,6	0	0,0	0	0,0	0	0,0	5	2,9
	Withdrawal syndrome	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2
	Total	22	12,9	21	12,4	7	4,1	1	0,6	14	8,2	65	38,2
Hepatobiliary disorders	Hepatic failure	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Hepatocellular injury	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	1	0,6	0	0,0	0	0,0	0	0,0	2	1,2
Infections and infestations	Clostridium difficile colitis	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Infection	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Urinary tract infection	1	0,6	2	1,2	0	0,0	0	0,0	0	0,0	3	1,8
	Total	1	0,6	3	1,8	1	0,6	0	0,0	0	0,0	5	2,9
Injury, poisoning and procedural complications	Procedural headache	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Subdural haematoma	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Urinary tract stoma complication	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	2	1,2	0	0,0	0	0,0	0	0,0	3	1,8
Investigations	Alanine aminotransferase increased	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Aspartate aminotransferase increased	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Body mass index decreased	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Body temperature increased	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Weight decreased	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2
	Total	4	2,4	0	0,0	2	1,2	0	0,0	0	0,0	6	3,5
Metabolism and nutrition disorders	Decreased appetite	1	0,6	1	0,6	0	0,0	0	0,0	0	0,0	2	1,2
	Fluid retention	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Hypercalcaemia	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Hypokalaemia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Hyponatraemia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Malnutrition	1	0,6	1	0,6	0	0,0	0	0,0	0	0,0	2	1,2
	Total	5	2,9	3	1,8	0	0,0	0	0,0	0	0,0	8	4,7
Musculoskeletal and connective tissue disorders	Back pain	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Coccydynia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Muscle spasms	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Musculoskeletal chest pain	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Pain in extremity	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6

		Grade											
		1		2		3		4		5		Total	
SOC (System Organ Class)	PT (Preferred Term)	N	%	N	%	N	%	N	%	N	%	N	%
	Soft tissue necrosis	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	3	1,8	2	1,2	0	0,0	0	0,0	6	3,5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Cancer pain	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Metastases to central nervous system	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Neoplasm malignant	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6	1	0,6
	Neoplasm progression	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2	2	1,2
	Tumour pain	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	2	1,2	0	0,0	3	1,8	6	3,5
Nervous system disorders	Amnesia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Balance disorder	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Coma	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6	1	0,6
	Depressed level of consciousness	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Dizziness	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Encephalopathy	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Headache	1	0,6	2	1,2	0	0,0	0	0,0	0	0,0	3	1,8
	Insomnia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Middle insomnia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Neuropathy peripheral	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Paraesthesia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Somnolence	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Tremor	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	8	4,7	5	2,9	1	0,6	0	0,0	1	0,6	15	8,8
Psychiatric disorders	Agitation	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Anxiety	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Completed suicide	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6	1	0,6
	Confusional state	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Delirium	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Depression	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Hallucination	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Sleep disorder	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Total	2	1,2	4	2,4	1	0,6	0	0,0	1	0,6	8	4,7
Renal and urinary disorders	Oliguria	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Pollakiuria	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2
Reproductive system and breast disorders	Genital pain	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Pelvic pain	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Total	0	0,0	1	0,6	1	0,6	0	0,0	0	0,0	2	1,2
Respiratory, thoracic and mediastinal disorders	Cough	2	1,2	0	0,0	0	0,0	0	0,0	0	0,0	2	1,2

		Grade											
		1		2		3		4		5		Total	
SOC (System Organ Class)	PT (Preferred Term)	N	%	N	%	N	%	N	%	N	%	N	%
	Dyspnoea	2	1,2	3	1,8	2	1,2	0	0,0	0	0,0	7	4,1
	Dyspnoea exertional	3	1,8	0	0,0	0	0,0	0	0,0	0	0,0	3	1,8
	Lung disorder	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6	1	0,6
	Oropharyngeal pain	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Pulmonary embolism	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Total	8	4,7	3	1,8	3	1,8	0	0,0	1	0,6	15	8,8
Skin and subcutaneous tissue disorders	Alopecia	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Decubitus ulcer	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Erythema	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Hyperhidrosis	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Night sweats	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Onycholysis	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Palmoplantar keratoderma	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Pruritus	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Skin ulcer	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Stasis dermatitis	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Uraemic pruritus	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Total	6	3,5	3	1,8	2	1,2	0	0,0	0	0,0	11	6,5
Surgical and medical procedures	Bladder catheterisation	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Preventive surgery	0	0,0	0	0,0	1	0,6	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	1	0,6	0	0,0	0	0,0	2	1,2
Vascular disorders	Blue toe syndrome	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6

9.2.2. Adverse Reactions

Table 98: Patients with at least one adverse reaction

		N	%
At least one adverse reaction	**No**	132	86,5
	Yes	23	13,5
	Total	170	100,0

Table 99: Adverse reactions

Subject ID	LLT (Lowest Level Term)	PT (Preferred Term)	Grade	Onset date	End date
33139577	Abdominal pain	Abdominal pain	2	Not available	2018-12-13
33139626	Abdominal pain	Abdominal pain	2	2018-10-27	2018-11-02
33139762	Abdominal pain	Abdominal pain	2	2018-12-13	2018-12-18
	Nausea	Nausea	1	2018-12-13	2018-12-18
33139898	Diarrhea	Diarrhoea	1	Not available	Not available
33139966	Abdominal pain	Abdominal pain	1	2019-02-21	2019-02-28
33139981	Diarrhea	Diarrhoea	Missing	2019-02-26	2019-02-26
33140006	Abdominal pain	Abdominal pain	Missing	2019-03-05	2019-03-18
	Abdominal cramps	Abdominal pain	Missing	2019-03-19	Missing
33140023	Abdominal cramps	Abdominal pain	Missing	2019-03-09	2019-03-10
33140105	Intestinal perforation	Intestinal perforation	5	2019-03-26	2019-03-26
33140107	Abdominal pain	Abdominal pain	1	2019-03-26	Not available
33140185	Abdominal pain	Abdominal pain	2	2019-04-02	2019-04-04
33140186	Nausea	Nausea	2	2019-04-09	2019-04-09
	Abdominal pain	Abdominal pain	2	2019-04-09	2019-04-09
33140190	Abdominal pain	Abdominal pain	2	2019-04-11	2019-04-13
	Flatulence	Flatulence	2	2019-04-11	2019-04-13
33140201	Diarrhea	Diarrhoea	2	2019-04-15	2019-04-18
33140306	Abdominal cramps	Abdominal pain	Missing	2019-05-11	2019-05-11
33140338	Diarrhea	Diarrhoea	2	Not available	Not available
33140458	Fatigue	Fatigue	2	2019-06-06	2019-06-18
33140552	Withdrawal symptom	Withdrawal syndrome	1	2019-06-20	2019-06-20
	Pollakiuria	Pollakiuria	1	2019-06-20	Missing
33140567	Diarrhea	Diarrhoea	2	2019-06-22	Missing
33140638	Intestinal cramps	Gastrointestinal pain	1	2019-07-16	Missing
33140760	Abdominal cramps	Abdominal pain	3	2019-09-23	2019-09-27
	Flatulence	Flatulence	3	2019-09-23	2019-09-27
33140800	Abdominal colic	Abdominal pain	1	2019-12-21	2019-12-21
33141127	Vertigo	Vertigo	1	2020-01-29	2020-04-30

Table 100: Adverse reactions by grade

		Grade											
		1		2		3		5		Not available		Total	
PT (Preferred Term)	**LLT (Lowest Level Term)**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Abdominal pain	**Abdominal colic**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Abdominal cramps	0	0,0	0	0,0	1	0,6	0	0,0	3	1,8	4	2,4
	Abdominal pain	2	1,2	6	3,5	0	0,0	0	0,0	1	0,6	9	5,3
	Total	3	1,8	6	3,5	1	0,6	0	0,0	4	2,4	14	8,2
Diarrhoea	**Diarrhea**	1	0,6	3	1,8	0	0,0	0	0,0	1	0,6	5	2,9
	Total	1	0,6	3	1,8	0	0,0	0	0,0	1	0,6	5	2,9
Fatigue	**Fatigue**	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
	Total	0	0,0	1	0,6	0	0,0	0	0,0	0	0,0	1	0,6
Flatulence	**Flatulence**	0	0,0	1	0,6	1	0,6	0	0,0	0	0,0	2	1,2
	Total	0	0,0	1	0,6	1	0,6	0	0,0	0	0,0	2	1,2
Gastrointestinal pain	**Intestinal cramps**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
Intestinal perforation	**Intestinal perforation**	0	0,0	0	0,0	0	0,0	1	0,6	0	0,0	1	0,6
	Total	0	0,0	0	0,0	0	0,0	1	0,6	0	0,0	1	0,6
Nausea	**Nausea**	1	0,6	1	0,6	0	0,0	0	0,0	0	0,0	2	1,2
	Total	1	0,6	1	0,6	0	0,0	0	0,0	0	0,0	2	1,2
Pollakiuria	**Pollakiuria**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
Vertigo	**Vertigo**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
Withdrawal syndrome	**Withdrawal symptom**	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6
	Total	1	0,6	0	0,0	0	0,0	0	0,0	0	0,0	1	0,6

9.2.3. Serious Adverse Events

A serious adverse event is any event that requires hospitalization, defined as an in-patient admission, regardless of length of stay (or prolongation of hospitalization) and occurred during the study must be reported as a serious adverse event, except for hospitalizations for the following reasons:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g. for social reasons such as the expected admission in a long-term care center).
- Surgical interventions or other procedures scheduled before entry into the study.

Table 101: Patients with at least one serious adverse event

		N	%
At least one serious adverse event	**No**	132	77,6
	Yes	38	22,4
	Total	170	100,0

Table 102: Patients with at least one serious adverse reaction

		N	%
At least one serious adverse reaction	**No**	168	98,8
	Yes	2	1,2
	Total	170	100,0

Table 103: SAE listing

Subject ID	LLT (Lowest Level Term)	Grade	Onset date	End date	Measure taken	Relation with medication	Outcome	Seriousness criteria
33139494	Asthenia	1	2018-09-06	2018-09-08	None	None	Recovered	Hospitalization
33139505	Fatigue	3	2018-09-04	2018-09-06	None	None	Recovered	Hospitalization
33139577	Disease progression	5	2018-11-09	2018-12-14	None	None	Death	Death
33139959	Cancer pain	3	2019-03-08	2019-03-28	None	None	Not recovered/ Ongoing*	Prolonged hospitalization
33139966	Tumor pain	3	2019-03-22	2019-04-08	None	None	Recovered	Hospitalization
33139993	Embolism pulmonary	3	2019-03-15	2019-03-21	None	None	Recovered	Hospitalization
33140023	Disease progression	5	2019-04-03	2019-04-03	None	Concomitant disease	Death	Death
33140088	Condition aggravated	4	2019-04-20	2019-04-30	None	Cancer	Recovered	Hospitalization
33140093	Disease progression	5	2019-03-21	2019-03-28	None	None	Death	Death
33140105	Intestinal perforation	5	2019-03-26	2019-03-26	Withdrawn naloxegol	Naloxegol	Death	Death
33140130	Disease progression	5	2019-04-08	2019-05-07	None	None	Death	Death
33140153	Fever	2	2019-04-08	2019-04-14	None	None	Recovered	Hospitalization
	Disease progression	5	2019-04-16	2019-05-01	None	None	Death	Death
33140179	Disease progression	5	2019-05-22	2019-05-27	None	None	Death	Death
33140180	Suicide	5	2019-04-06	2019-04-06	None	None	Death	Death
33140184	Disease progression	5	2019-05-13	2019-05-13	None	None	Death	Death
33140194	Pneumopathy	5	2019-05-09	2019-05-20	None	Concomitant disease	Death	Death
33140241	Disease progression	3	2019-06-08	2019-06-13	None	None	Recovered	Hospitalization
33140283	Dyspnea	3	2019-06-05	2019-06-12	None	None	Recovered with sequelae	Hospitalization
33140319	Pelvic pain	3	2019-05-16	2019-05-29	None	Bone metastasis	Recovered	Hospitalization
33140337	Disease progression	5	2019-05-25	2019-06-08	Interruption naloxegol	Concomitant disease	Death	Death*
33140567	Diarrhea	2	2019-06-22		Interruption naloxegol	Naloxegol	Not recovered/Ongoing	Medically important
33140594	Disease progression	5	2019-07-28	2019-07-28	None	None	Death	Death
33140604	Disease progression	5	2019-07-05	2019-07-26	Withdrawn naloxegol	None	Death	Death
33140676	Coma	5	2019-08-25	2019-09-01	Withdrawn	Concomitant	Death	Death

Subject ID	LLT (Lowest Level Term)	Grade	Onset date	End date	Measure taken	Relation with medication	Outcome	Seriousness criteria
					naloxegol	disease		
33140686	Tumor progression	5	2019-09-11	2019-09-11	None	None	Death	Death
33140704	Cancer	5	2019-09-02	Not available	None	None	Death	Death
33140721	Tumor progression	5	2019-10-03	2019-10-03	None	None	Death	Death
33140751	Chest wall pain	3	2019-07-30	2019-08-12	None	None	Recovered	Hospitalization
33140760	Duodenal obstruction	3	2019-09-17	2019-09-20	None	None	Recovered	Hospitalization
33140787	Swallowing difficult	3	2019-09-24	2019-10-10	None	None	Recovered	Hospitalization
33140792	Disease progression	5	2019-10-15	2019-10-15	None	None	Death	Death
33140800	Abdominal pain	3	2019-12-30	2020-01-08	None	Concomitant disease	Not recovered/ Ongoing*	Hospitalization
33140819	Disease progression	5	2019-10-19	2019-10-19	None	None	Death	Death
33140835	General physical health deterioration	3	2019-10-17		None	None	Not recovered/Ongoing	Prolonged hospitalization
33140932	Disease progression	5	2019-11-25	2019-11-25	None	None	Death	Death
33140995	Preventive surgery	3	2020-02-10	2020-02-13	None	None	Recovered	Hospitalization
33140996	Abdominal pain	3	2019-12-18	2019-12-26	None	None	Recovered	Hospitalization
33141136	Disease progression	5	2020-02-17	2020-02-17	None	None	Death	Death