

Table 1 Study endpoints

Primary endpoint

- Change in JPAC-QOL from baseline at 2 weeks

Key secondary endpoints

- Change in SBMs from baseline at 2 and 12 weeks

Other secondary endpoints

- Change in JPAC-QOL from baseline at 12 weeks
- Change in PAC-SYM from baseline at 2 and 12 weeks
- Change in CSS from baseline at 2 and 12 weeks
- Change in Rome IV from baseline at 2 and 12 weeks
- Change in BSFS from baseline at 2 and 12 weeks
- Change in SF-36 from baseline at 2 and 12 weeks

Safety endpoint

- Assessment of adverse events (AEs) that appeared from day 1 to 28 after treatment

Table 2 Japanese version of Patient Assessment of Constipation Quality of Life (PAC-QOL)

The following questions are designed to measure the impact constipation has had on your daily life over the past 2 weeks. For each question, please check one box.

The following questions ask about your symptoms related to constipation. During the past 2 weeks, to what extent or intensity have you...

	Not at all	A little bit	Moderately	Quite a bit	Extremely
	1	2	3	4	5
1. Felt bloated to the point of bursting?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Felt heavy because of your constipation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next few questions ask about how constipation affects your daily life. During the past 2 weeks, how much of the time have you...

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
	1	2	3	4	5
3. Felt any physical discomfort?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Felt the need to have a bowel movement but not been able to?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. Been embarrassed to be with other people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Been eating less and less because of not being able to have bowel movements?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next few questions ask about how constipation affects your daily life. During the past 2 weeks, to what extent or intensity have you...

	Not at all	A little bit	Moderately	Quite a bit	Extremely
	1	2	3	4	5
7. Had to be careful about what you eat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8. Had a decreased appetite?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9. Been worried about not being able to choose what you eat (for example, at a friend's house)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10. Been embarrassed about staying in the bathroom for so long when you were away from home?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
11. Been embarrassed about having to go to the bathroom so often when you were away from home?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
12. Been worried about having to change your daily routine (for example, traveling, being away from home)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next few questions ask about your feelings related to constipation. During the past 2 weeks, how much of the time have you...

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
	1	2	3	4	5
13. Felt irritable because of your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
14. Been upset by your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15. Felt obsessed by your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16. Felt stressed by your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
17. Felt less self-confident because of your condition?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
18. Felt in control of your situation?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next questions ask about your feelings related to constipation. During the past 2 weeks, to what extent or intensity have you...

- 19. Been worried about not knowing when you are going to be able to have a bowel movement?
- 20. Been worried about not being able to have a bowel movement?
- 21. Been increasingly bothered by not being able to have a bowel movement?

	Not at all	A little bit	Moderately	Quite a bit	Extremely
	1	2	3	4	5
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next questions ask about your life with constipation. During the past 2 weeks, how much of the time have you...

- 22. Been worried that your condition will get worse?
- 23. Felt that your body was not working properly?
- 24. Had fewer bowel movements than you would like?

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
	1	2	3	4	5
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

The next questions ask about your degree of satisfaction related to constipation. During the past 2 weeks, to what extent or intensity have you been...

- 25. Satisfied with how often you have a bowel movement?
- 26. Satisfied with the regularity of your bowel movements?

	Not at all	A little bit	Moderately	Quite a bit	Extremely
	1	2	3	4	5
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

27. Satisfied with the time it takes for food to pass through the intestines?
28. Satisfied with your treatment?

Table 3 Inclusion and exclusion criteria

Description of inclusion criteria
Males and females; 20–85 years of age
Patients who have not started opioid therapy
Patients who will commence opioid therapy for cancer pain
Patients capable of oral intake
Patients capable of reporting the patient reported outcomes (PRO)
Patients who are prospectively to stay in the stable pathological condition during the observation period
Patients who are able to provide written consent to participate in this research, follow instructions during participation, and undergo protocol-specified physical examinations and other examinations, and report their symptoms or events
Description of exclusion criteria
Patients with any contraindications listed on the package insert for magnesium oxide/naldemedine or with a history of hypersensitivity to any ingredients of them
Patients with a serious gastrointestinal structural anomaly (e.g: mechanical ileus), a disease that influences intestinal transit (e.g: paralytic ileus, peritoneal dissemination, peritoneal cancer, uncontrolled

hyper/hypothyroidism), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD, e.g: ulcerative colitis, Crohn's disease), active diverticular disease, pelvic disorders that cause constipation (e.g: uterine prolapse, rectal prolapse, myoma of the uterus that influences defecation). Or, patients decided by the doctor to have serious influence on gastrointestinal function (e.g: difficulty with oral intake), even if the disease written above are cured

Breastfeeding women or women with possible pregnancy

Patients who had undergone a surgery or a treatment that influences gastrointestinal function (e.g: nerve block) 28 days within the enrolment day, or patients planning to take them during the observation period

Table 4 Adverse events

Grade	Description
Grade 1 (mild)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2 (moderate)	Minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL

Grade 3 (severe)	Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4 (life-threatening)	Life-threatening consequences; urgent intervention indicated
Grade 5 (death)	Death related to AE
