

DESCRIPTION

INSTANTANEOUS INTESTINAL REGULATOR

5 Technical Field

The present invention relates to fast-acting intestinal regulators with little physical burden unlike conventional intestinal regulators. Specifically, the present invention relates to fast-acting intestinal regulators with little physical burden, which comprise a culture of propionic acid bacteria, or 1,4-dihydroxy-2-naphthoic acid (DHNA), or an analog thereof, as an active
10 ingredient.

Background Art

Fast-action (the property of working rapidly) is needed to relieve constipation, and as fast-acting purgatives (laxatives), those that improve fecal properties by expanding feces with
15 moisture in addition to inducing the desire to defecate (bulk-forming laxatives), and those that directly enhance intestinal movement (particularly, the contractile force of the intestine) (stimulant laxatives) and such have been known from before. These laxatives are used for symptomatic treatment, and individuals with a chronic tendency to become constipated need to take them frequently (use them continuously). However, continuous use of such laxatives
20 causes tolerance, and therefore they are not suitable for continuous ingestion or long-term intake. Furthermore, since these laxatives may induce side effects such as abdominal pain and diarrhea, their physical burden is great, and frequent intake particularly by the elderly, babies, infants, and sick people is difficult.

On the other hand, while fast-acting effects are weak, probiotics (for example, live
25 bacteria such as lactic acid bacteria and bifidobacteria) and prebiotics (for example, indigestible oligosaccharides, dietary fibers, and sterilized substances of a culture of microorganisms) are known as intestinal regulators that regulate the enteric environment when taken continuously. These intestinal regulators express intestine-regulating effects gently, and have a very low possibility to induce side effects such as abdominal pain and diarrhea, which are issues
30 associated with the above-mentioned laxatives.

Recently, there are many people, mostly women and the elderly, with a chronic tendency for constipation. Therefore, intestinal regulators for continuous and long-term ingestion or intake which have little physical burden and provide a sense of safety are desired. Regulating the enteric environment to promote natural defecation leads to maintenance of health and
35 improvement of QOL. Therefore, such a regulation is much needed and several functional foods with such effects as intestinal regulators are known.

For example, Profec (manufactured by Meiji, product name; “Profec” is a registered trademark of Meiji Co. Ltd.) is known as prebiotics and has been commercialized as “Onaka Katsuryoku Tablet (tablet containing Profec)” and “Onaka Katsuryoku Milk (milk beverage containing Profec)” (manufactured by Meiji; “Onaka Katsuryoku” is a registered trademark of Meiji Co., Ltd.), and such, that have been approved as foods for specified health uses. Profec is a fermented whey product produced using propionic acid bacteria (*Propionibacterium freudenreichii* ET-3 strain) isolated from Emmental cheese, and was developed as a material that contains components having an effect of promoting the growth of specifically bifidobacteria among major enteric bacteria (Non-patent Document 1). Intake of Profec for two to four weeks by humans has been shown to exhibit intestine-regulating effects (Non-patent Documents 2-4 and Patent Document 1). Subsequent studies identified 1,4-dihydroxy-2-naphthoic acid (DHNA) as the major participating ingredient contained in Profec that has the effect of promoting bifidobacterial growth. Furthermore, it has been elucidated that DHNA exhibits effects of improving/preventing colitis when administered to colitis model animals (Non-patent Document 5).

However, probiotics and prebiotics are known to have several issues, such as: (i) a fixed amount has to be ingested or taken (administered) continuously for one week or longer for expression of intestine-regulating effects (Patent Documents 2 and 3), (ii) among the intestine-regulating effects, bowel movement-improving effects (such as increase in stool count and increase in stool amount) are usually not very noticeable (Patent Document 2), and (iii) bowel movement-improving effects last for a short period of time, and those with a tendency for constipation must ingest or take (be administered) them continuously. More specifically, intestinal regulators that are fast-acting, persistent, and safe are hardly known at present.

Prior Art Documents

[Patent Documents]

[Patent Document 1] WO 2011/145737

[Patent Document 2] Japanese Patent Application *Kokai* Publication No. (JP-A) 2001-169749 (unexamined, published Japanese patent application)

[Patent Document 3] JP-A (*Kokai*) 2006-104121

[Non-patent Documents]

[Non-patent Document 1] Bioscience Microflora, Vol. 18(2), 73-80, 1999

[Non-patent Document 2] Bioscience Microflora, Vol. 21(2), 115-120, 2002

[Non-patent Document 3] Japanese Journal of Medicine and Pharmaceutical Science, Vol 49, 933-940, 2003

[Non-Patent Document 4] Journal of Intestinal Bacteriology, Vol. 18, 107-115, 2004

[Non-Patent Document 5] Gut 55, 681-688, 2005

Summary

[Problems to be Solved]

5 An objective of the present disclosure is to provide an intestinal regulator with little physical burden, which is highly safe, fast-acting, and persistent.

[Means for Solving the Problems]

The present disclosure is based on novel findings of fast-acting and persistent intestine-regulating effects of Profec, which were previously unknown.

10 Until now, the present inventors conducted many evaluations on Profec with regard to its intestine-regulating effects when Profec was taken for only several weeks at a time. As a result, intake of Profec for two to four weeks was shown to provide a certain effect of improving bowel movement (for example, Non-Patent Documents 3 and 4). In contrast, the present inventors evaluated for the first time, the intestine-regulating effects of Profec over time on subjects of a wide range of ages who are suffering from constipation. Surprisingly, the inventors discovered that significant bowel movement-improving
15 effects were seen one day after initiating Profec intake, and more remarkable bowel movement-improving effects were seen two days after intake. The inventors also found out that during the two-week period of Profec intake, this bowel movement-improving effects did not weaken, and these effects were maintained for at least two weeks after stopping Profec intake.

20 In one aspect, the present invention refers to the use of an intestinal regulator comprising a collagen peptide and a culture of propionic acid bacteria or a collagen peptide and DHNA in the manufacture of a medicament for improving constipation in patients of ages 18 to 64, wherein the propionic acid bacteria is selected from the group consisting of *Propionibacterium freudenreichii*, *Propionibacterium acidipropionici*, and *Propionibacterium jensenii*, wherein improvement of constipation is obtained within 7 days of administration of the medicament and
25 maintained for at least two weeks from after stopping administration of the medicament; and wherein the content of DHNA in the

medicament is 5 µg to 100 µg per day or the content of the culture of propionic acid bacteria in the medicament is 0.001 to 20wt%.

In another aspect, the present invention refers to the use of an intestinal regulator comprising a collagen peptide and a culture of propionic acid bacteria or a collagen peptide and DHNA in the manufacture of a medicament for improving mild constipation in patients of ages 18 to 64, wherein the propionic acid bacteria is selected from the group consisting of *Propionibacterium freudenreichii*, *Propionibacterium acidipropionici*, and *Propionibacterium jensenii*, wherein improvement of mild constipation is obtained within 7 days of administration of the medicament and maintained for at least two weeks from after stopping administration of the medicament, and wherein the content of DHNA in the medicament is 5 µg to 100 µg per day or the content of the culture of propionic acid bacteria in the medicament is 0.001 to 20wt%.

Basic characteristics and various embodiments of the present disclosure are provided below:

- [1] A fast-acting intestinal regulator comprising at least one component from among a culture of propionic acid bacteria, DHNA, or an analog thereof.
- [2] The fast-acting intestinal regulator of [1], wherein the propionic acid bacteria is *Propionibacterium freudenreichii*.
- [3] The fast-acting intestinal regulator of [1] or [2], which is a fast-acting bowel movement-improving agent.
- [4] the fast-acting intestinal regulator of any one of [1] to [3], wherein an intestine-regulating effect is obtained within seven days, preferably within two days, more preferably within one day after its intake (administration);
- [5] the fast-acting intestinal regulator of any one of [1] to [4], which maintains an intestine-regulating effect for (at least) one week, preferably 1.5 weeks, more preferably two weeks from after stopping its intake (administration);
- [6] the fast-acting intestinal regulator of any one of [1] to [5], wherein the intake (dose) per day

is 5 μg or more (for example 5 μg to 100 μg), preferably 6 μg or more (for example 6 μg to 50 μg), and more preferably 6.5 μg or more (for example 6.5 μg to 20 μg), when the converted amount (intake) of DHNA or an analog thereof is used as an indicator;

[7] the fast-acting intestinal regulator of any one of [1] to [6], wherein the content per single packaged form is 5 μg to 100 μg , preferably 6 μg to 50 μg , and more preferably 6.5 μg to 20 μg , when the converted amount (content) of DHNA or an analog thereof is used as an indicator;;

[8] the fast-acting intestinal regulator of any one of [1] to [7], which is taken (administered) together with a collagen peptide; and

[9] the fast-acting intestinal regulator of any one of [1] to [8], further comprising a collagen peptide.

The present disclosure further relates to the following embodiments:

[A-1] a method for producing a fast-acting intestinal regulator comprising the step of mixing (using) at least one component from among a culture of propionic acid bacteria, DHNA, or an analog thereof, wherein the propionic acid bacteria is preferably *Propionibacterium*

freudenreichii and the fast-acting intestinal regulator is preferably a fast-acting bowel movement-improving agent;

[A-2] the method for producing a fast-acting intestinal regulator of [A-1], wherein an intestine-regulating effect is obtained within seven days, preferably within two days, and more preferably within one day after intake (after administration) of the regulator;

[A-3] the method for producing a fast-acting intestinal regulator of [A-1] or [A-2], wherein an intestine-regulating effect is maintained for (at least) one week, preferably 1.5 weeks, and more preferably two weeks from after stopping intake (administration) of the regulator;

[A-4] the method for producing a fast-acting intestinal regulator of any one of [A-1] to [A-3], wherein the intake (dose) of the regulator per day is 5 μg or more (for example 5 μg to 100 μg), preferably 6 μg or more (for example 6 μg to 50 μg), and more preferably 6.5 μg or more (for example 6.5 μg to 20 μg), when the converted amount (intake) of DHNA or an analog thereof, is used as an indicator; and

[A-5] the method for producing a fast-acting intestinal regulator of any one of [A-1] to [A-4], wherein the content of the regulator per single packaged form is 5 μg to 100 μg , preferably 6 μg to 50 μg , and more preferably 6.5 μg to 20 μg , when the converted amount (content) of DHNA or an analog thereof is used as an indicator.

The present disclosure further relates to the following embodiments:

[B-1] use of a culture of propionic acid bacteria or DHNA or an analog thereof in the manufacture of a fast-acting intestinal regulator, wherein the propionic acid bacteria is preferably *Propionibacterium freudenreichii* and the fast-acting intestinal regulator is preferably a fast-acting bowel movement-improving agent;

[B-2] the use of [B-1], wherein an intestine-regulating effect is obtained within seven days, preferably within two days, and more preferably within one day after intake (after administration) of the regulator;

5 [B-3] the use of [B-1] or [B-2], wherein an intestine-regulating effect is maintained for (at least) one week, preferably 1.5 weeks, and more preferably two weeks from after stopping intake (administration) of the regulator;

[B-4] the use of any one of [B-1] to [B-3], wherein the intake (dose) of the regulator per day is 5 μ g or more (for example 5 μ g to 100 μ g), preferably 6 μ g or more (for example 6 μ g to 50 μ g), and more preferably 6.5 μ g or more (for example 6.5 μ g to 20 μ g), when the converted amount
10 (intake) of DHNA or an analog thereof is used as an indicator; and

[B-5] the use of any one of [B-1] to [B-4], wherein the content of the regulator per single packaged form is 5 μ g to 100 μ g, preferably 6 μ g to 50 μ g, and more preferably 6.5 μ g to 20 μ g, when the converted amount (content) of DHNA or an analog thereof is used as an indicator.

The present disclosure further relates to the following embodiments:

15 [C-1] a culture of propionic acid bacteria or DHNA or an analog thereof for use in developing a fast-acting intestine-regulating effect, wherein the propionic acid bacteria is preferably *Propionibacterium freudenreichii* and the fast-acting intestine-regulating effect is preferably a fast-acting bowel movement-improving effect;

[C-2] the culture of propionic acid bacteria or DHNA or an analog thereof of [C-1], wherein an
20 intestine-regulating effect is obtained within seven days, preferably within two days, and more preferably within one day after intake (after administration) of the regulator;

[C-3] the culture of propionic acid bacteria or DHNA or an analog thereof of [C-1] or [C-2], wherein an intestine-regulating effect is maintained for (at least) one week, preferably 1.5 weeks, and more preferably two weeks from after stopping intake (administration) of the regulator;

25 [C-4] the culture of propionic acid bacteria or DHNA or an analog thereof of any one of [C-1] to [C-3], wherein the intake (dose) of the regulator per day is 5 μ g or more (for example 5 μ g to 100 μ g), preferably 6 μ g or more (for example 6 μ g to 50 μ g), and more preferably 6.5 μ g or more (for example 6.5 μ g to 20 μ g), when the converted amount (intake) of DHNA or an analog thereof is used as an indicator; and

30 [C-5] the culture of propionic acid bacteria or DHNA or an analog thereof of any one of [C-1] to [C-4], wherein the content of the regulator per single packaged form is 5 μ g to 100 μ g, preferably 6 μ g to 50 μ g, and more preferably 6.5 μ g to 20 μ g, when the converted amount (content) of DHNA or an analog thereof is used as an indicator.

The present disclosure further relates to the following embodiment:

35 [D-1] a method for developing a fast-acting intestine-regulating effect comprising the step of making a subject take (administering to a subject) an effective amount of at least one component

from among a culture of propionic acid bacteria, DHNA or an analog thereof, wherein the propionic acid bacteria is preferably *Propionibacterium freudenreichii* and the fast-acting intestine-regulating effect is preferably a fast-acting bowel movement-improving effect;

[D-2] the method for developing a fast-acting intestine-regulating effect of [D-1], wherein the intestine-regulating effect is obtained within seven days, preferably within two days, and more preferably within one day after intake (after administration) of the regulator;

[D-3] the method for developing a fast-acting intestine-regulating effect of [D-1] or [D-2], wherein the intestine-regulating effect is maintained for (at least) one week, preferably 1.5 weeks, and more preferably two weeks from after stopping intake (administration) of the regulator;

[D-4] the method for developing a fast-acting intestine-regulating effect of any one of [D-1] to [D-3], wherein the intake (dose) of the regulator per day is 5 μ g or more (for example 5 μ g to 100 μ g), preferably 6 μ g or more (for example 6 μ g to 50 μ g), and more preferably 6.5 μ g or more (for example 6.5 μ g to 20 μ g), when the converted amount (intake) of DHNA or an analog thereof is used as an indicator; and

[D-5] the method for developing a fast-acting intestine-regulating effect of any one of [D-1] to [D-4], wherein the content of the regulator per single packaged form is 5 μ g to 100 μ g, preferably 6 μ g to 50 μ g, and more preferably 6.5 μ g to 20 μ g, when the converted amount (content) of DHNA or an analog thereof is used as an indicator.

In [D-1] to [D-5], medical practices (practices requiring a physician's prescription) are preferably excluded.

[Effects of the Invention]

As described above, probiotics and prebiotics have been generally known to express intestine-regulating effects by regulating the enteric environment when they are taken continuously.

Therefore, they have been recognized as components used or intended to be used mainly for preventing constipation. Propionic acid bacteria cultures, or DHNA or an analog thereof which is the active ingredient of the fast-acting intestinal regulator of the present disclosure, were hitherto known to be prebiotics, but surprisingly, it was revealed for the first time that bowel movement-improving effects developed in a short period of time, which is within one day after intake, and more remarkable bowel movement-improving effects were seen within two days after intake. In addition, the fast-acting intestinal regulators of the present disclosure can be produced by mixing a component (food material, etc.) that has been taken by (administered to) humans as food or such. Therefore, a high level of safety is already guaranteed for the fast-acting intestinal regulators of the present disclosure, and they can thus be taken even ceaselessly (continuously). Thus, it became clear that the fast-acting intestinal regulators of the present disclosure can be provided as novel means with little physical burden for

obtaining fast-acting intestine-regulating effects, since they combine a plurality of advantageous effects; the fast-acting property of conventional laxatives and persistence and safety of conventional probiotics and prebiotics.

5 Brief Description of the Drawings

Fig. 1 shows a graph indicating the stool frequency of the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

10 Fig. 2 shows a graph indicating the change over time in the mean stool count of the subjects. "Wm-n" means day n of week m, and for example, W3-1 (day 1 of week 3) means the first day after intake of the test diet.

Fig. 3 shows a graph indicating the change over time in the mean stool amount of the subjects. "Wm-n" means day n of week m, and for example, W3-1 (day 1 of week 3) means the first day after intake of the test diet.

15 Fig. 4 shows a graph indicating the difficulty in defecation by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

20 Fig. 5 shows a graph indicating the time taken for defecation by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

Fig. 6 shows a graph indicating the change in sensation during defecation by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

25 Fig. 7 shows a graph indicating the degree of satisfaction regarding stool frequency by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

Fig. 8 shows a graph indicating the degree of satisfaction regarding the time taken for defecation by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

30 Fig. 9 shows a graph indicating the degree of satisfaction regarding stool properties by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

35 Fig. 10 shows a graph indicating the degree of satisfaction regarding stool habit by the subjects. "*" and "*Δ" indicate significant differences at $p < 0.01$ and $p < 0.05$, respectively, compared to the second week (week 2).

Fig. 11 shows a graph indicating the distribution of days when the subjects felt the

intestine-regulating effects. The horizontal axis shows the number of days after intake of the test diet, and the day of intake is defined as Day 0. For each day after intake of the test diet, the bar graph shows the number of subjects who felt the intestine-regulating effects for the first time, and the line graph shows the cumulative proportion of subjects who felt the intestine-regulating effects.

Mode for Carrying Out the Invention

The present invention will be described in detail below. However, the present invention is not limited to the following preferred embodiments, and can be altered arbitrary within the scope of the present invention.

The present invention provides fast-acting intestinal regulators comprising at least one active ingredient from among a culture of propionic acid bacteria, DHNA, or an analog thereof.

The term "intestine-regulating effect" as used herein includes bowel movement-improving effects, constipation-improving effects, enteric environment-improving effects, and stool property-improving effects, and is preferably a bowel movement-improving effect. Therefore, the term "intestinal regulator" as used herein includes bowel movement-improving agents, constipation-improving agents, enteric environment-improving agents, and stool property-improving agents, and is preferably a bowel movement-improving agent. The term "improvement of bowel movement" as used herein means increase in stool count, increase in stool amount, improvement of difficulty in defecation, shortening of time taken for defecation, improvement of sensation during defecation, improvement of stool frequency, improvement of stool properties, and/or improvement of stool habits, and may also be expressed as "promotion of bowel movement".

The term "fast-acting" as used herein means the property of developing a certain effect within seven days, within six days, within five days, within four days, or within three days after intake (after administration), preferably within two days after intake, and more preferably within one day after intake. The phrase "developing a fast-acting intestine-regulating effect" may also be expressed as "developing an intestine-regulating effect in a short period of time". Similarly, the phrase "improving in a short period of time" means improving a condition within seven days, within six days, within five days, within four days, within three days after intake (after administration), or preferably within two days after intake, and more preferably within one day after intake. Furthermore, the term "persistence" as used herein means the property of maintaining a certain effect for at least one week, preferably 1.5 weeks, and more preferably two weeks from stopping intake (administration). Here, the phrase "maintaining a certain effect" means that the effect after stopping intake of a certain (active) component is maintained at 30% or more, preferably 50% or more, and more preferably 70% or more in comparison to the effect

during intake. The term "intake" as used herein may also be expressed as "administration".

The term "fast-acting intestinal regulator" as used herein not only means pharmaceuticals or quasi-drugs used to express fast-acting intestine-regulating effects, but also means dietary supplements, foods with health claims (foods for specified health uses or foods with nutrient function claims), functional foods such as supplements, as well as food additives and such.

The fast-acting intestinal regulators of the present invention are characterized by having a little physical burden. Therefore, the fast-acting intestinal regulators of the present invention can be used for individuals of a wide range of ages who have a tendency for constipation. More specifically, they may be used favorably by women, the elderly, babies, infants, or sick people (patients) for whom the use of conventional laxatives is difficult or impossible since the physical burden is not small. Furthermore, since improved cosmetic effects can be expected from the fast-acting intestinal regulators of the present invention, they may be used favorably by women.

The term "little physical burden" as used herein means that intake of a certain (active) component does not lead to worsening of the difficulty of defecation, does not lower the satisfaction towards stool frequency, time taken for defecation, stool properties, or stool habits, or does not increase the degree or frequency of side effects such as abdominal pain or diarrhea. Furthermore, the term "little physical burden" means that intake of a certain (active) component results in a low degree or frequency of side effects such as abdominal pain or diarrhea, or leads to mild or no such side effects. Therefore, the fast-acting intestinal regulators of the present invention are preferably fast-acting intestinal regulators with a low degree or frequency of side effects, and more preferably fast-acting intestinal regulators without any side effects.

In one embodiment, the fast-acting intestinal regulators of the present invention comprise a culture of propionic acid bacteria. Propionic acid bacteria refers to Gram-positive anaerobic bacteria belonging to the genus *Propionibacterium*, which are microorganisms that produce propionic acid in an anoxic manner from carbohydrates. Specifically, cultures of the following microorganisms can be mixed into (added to) the fast-acting intestinal regulators of the present invention. More specifically, the microorganisms are *Propionibacterium freudenreichii*, *Propionibacterium thoenii* (*P. thoenii*), *Propionibacterium acidipropionici* (*P. acidipropionici*), *Propionibacterium jensenii* (*P. jensenii*), or such. These propionic acid bacteria are microorganisms used for cheese production. Furthermore, the following microorganisms may also be shown as propionic acid bacteria. More specifically, the microorganisms are *Propionibacterium avidum* (*P. avidum*), *Propionibacterium acnes* (*P. acnes*), *Propionibacterium lymphophilum* (*P. lymphophilum*), or *Propionibacterium granulosam* (*P. granulosam*).

Methods for isolating these propionic acid bacteria from nature or fermented milk are known. The propionic acid bacteria can be those used in Swiss cheese production and such.

A culture of propionic acid bacteria in the present invention refers to a material in which propionic acid bacteria such as those mentioned above are cultured under appropriate culturing conditions. Methods for culturing propionic acid bacteria are known. When culturing propionic acid bacteria, the conditions described in WO 03/016544 A1 and such may be applied.
5 For example, a culture of propionic acid bacteria can be obtained by inoculating *Propionibacterium freudenreichii* into a suitable medium, and culturing them under conditions that allow proliferation of propionic acid bacteria.

After culturing is completed, a culture of propionic acid bacteria may be mixed with other ingredients (materials, etc.) after sterilizing it, or alternatively, a culture of propionic acid
10 bacteria may be sterilized after it is mixed with other ingredients (materials, etc.), to produce the fast-acting intestinal regulators of the present invention. For example, in the case of cow milk, bactericidal methods and such are established by the ministerial ordinance on cow milk, and low-temperature long-time pasteurization, high-temperature short-time pasteurization, or ultrahigh-temperature (flash) pasteurization can be used as a general heat sterilization treatment.

15 Bactericidal methods or heat sterilization treatments equivalent to those used for cow milk can be applied to cultures of propionic acid bacteria or fast-acting intestinal regulators comprising them that are disclosed in the present invention. These heat sterilization treatments may be batch methods (in batch units) or may be continuous methods. At that time, the treatment temperature and treatment time may differ depending on the respective heat
20 sterilization treatment, but they are selected from the ranges of, preferably 0.1 seconds to one hour at 60°C to 150°C, more preferably 0.5 seconds to 45 minutes at 70°C to 150°C, even more preferably 1 second to 30 minutes at 80°C to 150°C, and the like depending on the above-mentioned bactericidal method. When sterilizing a culture of propionic acid bacteria, it is desirable to maintain the quantity of dissolved oxygen in the treatment solution at a reduced
25 condition. Thus, during heat sterilization treatment, it is preferable to continuously maintain the culture of propionic acid bacteria or the fast-acting intestinal regulator comprising it in an inert gas atmosphere and/or to inject (bubble) an inert gas into the culture of propionic acid bacteria or the fast-acting intestinal regulator comprising it, if desired. Examples of inert gas include nitrogen gas, argon gas, and carbon dioxide gas. In particular, nitrogen gas is desirable
30 since it is abundant in the air, its cost is relatively low, its safety is confirmed, and it does not affect the flavor and quality of foods and drinks. Alternatively, during heat sterilization treatment, it is preferable to maintain the culture of propionic acid bacteria or the fast-acting intestinal regulator comprising it under a vacuum (reduced pressure) state atmosphere, and/or to pass the culture of propionic acid bacteria or the fast-acting intestinal regulator comprising it
35 through a vacuum state atmosphere, if desired. An example of a vacuum state is, for example, reduced-pressure deaeration treatment.

The present inventors confirmed that the fast-acting intestine-regulating effect is maintained in the sterilized culture of propionic acid bacteria. That is, in the present invention, the fast-acting intestine-regulating effect of the culture of propionic acid bacteria is maintained even after the culture is sterilized. Typically, the effect of microorganisms (such as lactic acid bacteria) on a host depends on the activity of viable bacteria. There are many reports that probiotics and prebiotics improve the enteric environment and activate the immune system. Generally, probiotics refers to microorganisms that provide beneficial effects in a host when introduced into the intestines of the host in a viable condition. In contrast to probiotics, prebiotics refers to a substance that provides beneficial effects to the host by acting on microorganisms that originally inhabit the intestines. For example, several types of microorganisms (such as lactic acid bacteria and bifidobacteria) have been reported as probiotics that show intestine-regulating effects in human tests. However, since these microorganisms function as probiotics and act as viable bacteria, their production and quality control are not easy. Furthermore, formulations of viable bacteria generally have limitations in their preservative properties. For example, even if a formulation of viable bacteria is stored at a low temperature after production, it often cannot maintain its original activity (stability) for a long period of time.

In contrast to probiotics of conventional viable microorganisms (such as lactic acid bacteria and bifidobacteria), the culture of propionic acid bacteria of the present invention not only functions as probiotics but also functions as prebiotics. Here, in the sterilized culture of propionic acid bacteria of the present invention (prebiotics), the activity of the microorganisms (propionic acid bacteria) is stopped and its quality does not change. Therefore, the fast-acting intestine-regulating effects of prebiotics such as the culture of propionic acid bacteria of the present invention can be stably maintained. That is, since the cultures of propionic acid bacteria or the fast-acting intestinal regulators comprising them that are disclosed in the present invention are prebiotics that can also act as killed bacteria, their production and quality control are easy. Furthermore, formulations and such based on the present invention can maintain its original activity (stability) for a long period of time even when stored at a normal temperature. Furthermore, typically, when an effect by oral administration is anticipated, the effect often depends on the action of viable microorganisms (such as lactic acid bacteria and bifidobacteria) and the influence of gastric acid must be considered. This is because gastric acid reduces live microorganisms and a sufficient number of viable bacteria cannot be delivered into the intestines. On the other hand, when an effect by oral administration is anticipated in the present invention, a sufficient fast-acting intestine-regulating effect can be achieved, since the effect does not depend on the activity of live propionic acid bacteria alone, and the influence of gastric acid does not need to be considered.

The culture or sterilized culture of propionic acid bacteria of the present invention can

be processed into any form, such as liquid, paste, gel, powder, granule, or solid. For example, a suitable excipient may be added to (mixed with) the culture or sterilized culture of propionic acid bacteria of the present invention so that the solid content concentration becomes 30% to 40%.

This can be powdered by spray-drying or freeze-drying. Here, known excipients can be used,

5 and examples include powdered skim milk, whey powder, raw starch, dextrin, and such. In addition, WPC, WPI, and modified starch can also be used if desired. Furthermore, known methods can be used for spray-drying or freeze-drying, and for example, a method of spray-drying or a method of freeze-drying a culture or sterilized culture of propionic acid bacteria of the present invention as it is can be used. Alternatively, a method that spray dries or

10 freeze dries a culture or sterilized culture of propionic acid bacteria of the present invention after mixing it with a reduced excipient solution and concentrating it until the solid content concentration reaches 30% to 40% can be used. The dried product (powders, granules, and such) of the culture or sterilized culture of propionic acid bacteria of the present invention can be

stably preserved for a long period of time by performing a deoxygenation treatment (nitrogen sealing, addition of deoxygenating agent, and such) when filling it into packages and containers.

15 Furthermore, it can be processed into a triturated formulation (0.2% triturate) for easy use in food. As the processed starch for the excipients, one can use, for example, in addition to

dextrin, acetylated adipic acid cross-linked starch, acetylated phosphoric acid cross-linked starch, acetylated oxidized starch, starch sodium octenylsuccinate, acetate starch, oxidized starch,

20 hydroxypropyl starch, hydroxypropylated phosphoric acid cross-linked starch, phosphoric monoesterified phosphoric acid cross-linked starch, phosphorylated starch, and phosphoric acid cross-linked starch. Furthermore, the culture or sterilized culture of propionic acid bacteria of the present invention may be taken together with collagen peptides, or may be formulated together with collagen peptides.

25 A culture of propionic acid bacteria is typically known to have the effect of promoting lactic acid bacterial proliferation. A culture of propionic acid bacteria having such an effect, or a processed product thereof (sterilized products, condensed products, dried products, and such) is called a "bifidogenic growth stimulator (BGS)". As long as the BGS has fast-acting intestine-regulating effects, various components (materials, etc.) can be used as a culture of propionic acid bacteria of the present invention.

30 As a culture of propionic acid bacteria of the present invention, a whey fermentation product produced by propionic acid bacteria is preferred. For example, a culture of propionic acid bacteria obtained by fermenting reduced whey (a solution of whey powder) by *Propionibacterium freudenreichii* ET-3 strain which produces BGS can be used (included) as an active ingredient in the fast-acting intestine regulator of the present invention. A culture of propionic acid bacteria containing BGS is also called "Profec". Profec specifically increases

bifidobacterium in human intestines, and thus, it is approved as an effective food ingredient for specified health use (ILSI, No.80, 5-13(2004)). As compositions which contain "Profec", B. G. S. powder (product name; manufactured by Meiji Co., Ltd.), Onaka Katsuryoku tablet, and Onaka Katsuryoku milk (manufactured by Meiji Co., Ltd.; the product name: "Onaka Katsuryoku" is a registered trademark of Meiji Co., Ltd.) are commercially available. Therefore, "B. G. S. powder", "Onaka Katsuryoku tablet" or "Onaka Katsuryoku milk" can be also used as the fast-acting intestinal regulator of the present invention. A culture of propionic acid bacteria (a whey fermentation product produced by propionic acid bacteria) has been known to show an excellent intestinal regulating effect which is developed through long-term and continuous use. However, a culture of propionic acid bacteria, which is a prebiotic, was not known to show a fast-acting intestinal regulating effect following short-time use.

In particular, BGS included in Profec is 1,4-dihydroxy-2-naphthoic acid (DHNA), 2-amino-3-carboxy-1,4-naphthoquinone (ACNQ), and such. DHNA is a biosynthetic intermediate of vitamin K2 (menaquinone) in microorganisms. These DHNA and ACNQ promote proliferation of bifidobacterium by efficiently reoxidizing NADH produced in the process of bifidobacterium energy metabolism. Therefore, as a culture of propionic acid bacteria of the present invention, either or more than one of the following components (i) or (i') and (ii) or (ii') may be used. Specifically, the present invention provides a fast-acting intestinal regulator, which comprises as an active ingredient either or both of: (i) 1,4-dihydroxy-2-naphthoic acid (DHNA); and (ii) 2-amino-3-carboxy-1,4-naphthoquinone (ACNQ).

Methods for producing DHNA and ACNQ are already established, and those skilled in the art can easily synthesize and obtain them based on known documents and such. For example, DHNA can be synthesized according to the method described in JP-A (*Kokai*) 2007-284449 and such, but methods are not limited thereto. ACNQ can be synthesized according to the methods described in JP-A (*Kokai*) H07-289273, Japanese Patent No. 3265193, JP-A (*Kokai*) 2003-089683, Japanese Patent No. 4072430, Japanese Patent No. 3532226, and such, but the methods are not limited thereto. Therefore, these DHNA and ACNQ can be used as they are as the fast-acting intestinal regulator of the present invention by mixing these synthetics or a fractionated component of their active ingredients. Alternatively, these DHNA and ACNQ can be purified and then used as the fast-acting intestinal regulator of the present invention.

The present invention provides fast-acting intestinal regulators, which comprise as an active ingredient either one or both of (i') a DHNA analog and (ii') an ACNQ analog. Examples of such a DHNA analog and an ACNQ analog include 1,4-naphthoquinone, 2-methyl-1,4-naphthoquinone, 4-amino-2-methyl-1-naphthol, and

2-amino-3-chloro-1,4-naphthoquinone, but are not limited thereto. These DHNA analogs and ACNQ analogs are known to be produced in the culture of microorganisms used to produce fermented milk according to, for example, the method of JP-A (Kokai) H07-289273. Therefore, by mixing a culture of these microorganisms or a fractionated component of its active ingredients, such DHNA analogs and ACNQ analogs can be used as they are as the fast-acting intestinal regulators of the present invention. Alternatively, these DHNA analogs or ACNQ analogs can be purified and then used as a fast-acting intestinal regulator of the present invention, or they may be purified together with DHNA and ACNQ and then used as a regulator.

The dose (intake) per day for a human (adult) of a fast-acting intestinal regulator of the present invention which comprises the above-mentioned components (i) or (i') and/or (ii) or (ii'), is generally in the range of 0.01 $\mu\text{g/kg}$ body weight to 100 mg/kg body weight, when the converted amount (intake) of DHNA or an analog thereof included in the culture of propionic acid bacteria is used as an indicator. However, regarding the dose (intake) per day for a human (adult) of a fast-acting intestinal regulator of the present invention, a lower dose is sufficient in some cases, while a higher dose may be necessary in others, depending on the age, body type, gender, and such of the individual. The intake (dose) per day of a fast-acting intestinal regulator of the present invention is not particularly limited, but it is, for example, 5 μg or more (for example 5 μg to 100 μg), preferably 6 μg or more (for example 6 μg to 50 μg), and more preferably 6.5 μg or more (for example 6.5 μg to 20 μg), when the converted amount (intake) of DHNA or an analog thereof is used as an indicator. The intake (dose) per day of a fast-acting intestinal regulator of the present invention is, for example, 0.5 mg or more (for example 0.5 mg to 10 mg), preferably 0.6 mg or more (0.6 mg to 5 mg), and more preferably 0.65 mg or more (0.65 mg to 2 mg), when the converted amount (intake) of a culture of propionic acid bacteria is used as an indicator.

Regarding the fast-acting intestinal regulators of the present invention which comprise the above-mentioned components (i) or (i') and/or (ii) or (ii'), the content per single packaged form for a human (adult) is generally in the range of 0.01 $\mu\text{g/kg}$ body weight to 100 mg/kg body weight, when the converted amount (content) of DHNA or an analog thereof included in the propionic acid bacterial culture is used as an indicator. However, regarding the content of a fast-acting intestinal regulator of the present invention per single packaged form for a human (adult), a lower dose is sufficient in some cases, while a higher dose may be necessary in other cases, depending on the age, body type, gender, and such of the human individual. The content of a fast-acting intestinal regulator of the present invention per single packaged form is not particularly limited, but it is, for example, 5 μg to 100 μg , preferably 6 μg to 50 μg , and more preferably 6.5 μg to 20 μg , when the converted amount (content) of DHNA or an analog thereof is used as an indicator. The content of the fast-acting intestinal regulator of the present

invention per single packaged form is, for example, 0.5 mg to 10 mg, preferably 0.6 mg to 5 mg, and more preferably 0.65 mg to 2 mg, when the converted amount (content) of a culture of propionic acid bacteria is used as an indicator.

The administration frequency (intake frequency) of a fast-acting intestinal regulator of the present invention to a human (adult) may be, for example, divided into several times (two to four times, or such) per day. The dose (intake) per day for a human (adult) individual means the amount needed to develop a fast-acting intestine-regulating effect, and it can be set by considering the condition of the individual receiving the administration (the individual who is subjected to the intake), such as age, body type, gender, and such of the individual, administration route, and the degree of the intestine-regulating effect that is actually expected. In this case, the route of administration (route of intake) of the fast-acting intestinal regulator of the present invention for a human (adult) is preferably oral administration (oral intake) or enteral administration (enteral intake), and oral administration (oral intake) is more preferred.

A fast-acting intestinal regulator of the present invention can be prepared by mixing a culture of propionic acid bacteria, for example, at 0.001 to 20 wt. %, preferably 0.01 to 15 wt. %, and more preferably 0.05 to 10 wt. %. The fast-acting intestinal regulator of the present invention can be processed into any dosage form such as liquid, paste, gel, powder, granules, or solid form. Specifically, it can be formulated into tablets, capsules, granules, powders, syrups, and such. These various formulations can be formulated routinely by applying to the main agent, known additives that may be commonly used in the field of pharmaceutical formulation such as excipients, binders, disintegrants, lubricants, flavoring agents, solubilizing agents, suspending agents, coating agents, solvents, isotonizing agents, antioxidants, and stabilizing agents (for example, vitamin C). The fast-acting intestinal regulator of the present invention can be prepared or provided by mixing (blending) a culture of propionic acid bacteria with a component (fermented milk components and such) suitable for oral administration (oral intake), or with a pharmaceutically acceptable carrier. Alternatively, the fast-acting intestinal regulator of the present invention can be prepared or provided by adding (dispersing) a culture of propionic acid bacteria in a component (fermented milk components, and such) suitable for oral administration (oral intake), or in a pharmaceutically acceptable carrier. At this time, suitable amount of vitamins, minerals, organic acids (including fatty acids such as short-chain fatty acids), carbohydrates, amino acids, peptides (for example, collagen peptides), and such may be mixed.

As described above, the present inventors discovered that fast-acting intestine-regulating effects are expressed in humans who have taken (have been orally administered or such) at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof. More specifically, the present invention relates to fast-acting intestinal regulators comprising at

least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof.

Furthermore, the present invention relates to methods for developing fast-acting intestine-regulating effects comprising the step of making an animal take (for example, orally administering to an animal) at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof. In the present invention, the animal includes mammals, birds, amphibians, and reptiles, but is preferably a mammal, and more preferably a human individual, and even more preferably a female human individual.

The present invention also relates to use of at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof in the manufacture of a fast-acting intestinal regulator.

Alternatively, the present invention relates to use of at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof in expressing fast-acting intestine-regulating effects.

Additionally, the present invention relates to methods for producing fast-acting intestinal regulators, which comprise the step of using at least one component selected from among (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof. Furthermore, the present invention relates to at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof, which is to be used for developing fast-acting intestine-regulating effects.

The fast-acting intestinal regulators of the present invention can be used in the form of pharmaceuticals, quasi-drugs, dietary supplements, foods with health claims (foods for specified health uses or foods with nutrient function claims), functional foods (supplements and such), other foods, food additives, and such. Tablets are a preferred embodiment for supplements and such, since they provide good preservation properties and ensure an effective amount of intake. The term "foods" as used herein includes "drinks". Furthermore, the fast-acting intestinal regulators of the present invention can be used in pharmaceuticals and foods and drinks (formula milk for babies, food such as powdered milk for young children, powdered milk for nursing women, and such) that have biological standards. The fast-acting intestinal regulators of the present invention may include, for example, a suspension of propionic acid bacteria, cell bodies of propionic acid bacteria, a culture supernatant of propionic acid bacteria (including medium components), a fermentation product from propionic acid bacteria, and such, in various forms.

The fast-acting intestinal regulators of the present invention can be taken (orally administered) alone, or it can be taken (orally administered) in combination with (by mixing

with) other components commonly used in pharmaceuticals or foods. During this intake, combined use of other compounds, microorganisms, or such that particularly have intestine-regulating effects is effective in the improvement and development of fast-acting intestine-regulating effects.

5 The fast-acting intestinal regulators of the present invention may be in the form of foods such as cow milk, dairy products, soft drinks, powder drinks, fermented milk, lactobacillus beverages, acidic beverages, yogurt, cheese, bread, biscuits, crackers, pizza crusts, formula milk, fluid diets, food for the sick, nutritional food, frozen food, food compositions, processed food, and other commercially available food. The fast-acting intestinal regulators of the present
10 invention in the form of acidic pharmaceuticals or foods can have their pH set to, for example, pH 2 to 6, or preferably pH 3 to 5.

As shown later in the Examples, the fast-acting intestinal regulators of the present invention showed fast-acting intestine-regulating effects through intake as an agent containing a culture of propionic acid bacteria. Therefore, preferred embodiments of the present invention
15 include a functional food or a pharmaceutical composition produced by mixing in at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof.

More specifically, the present invention relates to methods for producing a functional food or a pharmaceutical composition which develops fast-acting intestine-regulating effects, comprising the step of mixing at least one component selected from the group consisting of (a) a
20 culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof with a functional food or a pharmaceutically acceptable carrier. Alternatively, the present invention relates to methods for imparting the ability to develop fast-acting intestine-regulating effects to a functional food, comprising the step of mixing at least one
25 component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof with a functional food.

Furthermore, the present invention relates to pharmaceutical compositions prepared by mixing at least one component selected from the group consisting of (a) a culture of propionic acid bacteria, (b) DHNA or an analog thereof, and (c) ACNQ or an analog thereof with a
30 pharmaceutically acceptable carrier. When further mixing additional components (for example, collagen peptides), the composition may be prepared by using carbohydrates (for example, maltodextrin) and such as a carrier and homogeneously blending them, and vitamin C or such may be mixed in as a stabilizing agent. The fast-acting intestinal regulators of the present invention can be prepared by mixing a protein derived from a culture of propionic acid bacteria
35 such that the proportion thereof is, for example, 1 wt. % or more of the carbohydrate, preferably 10 wt. % or more of the carbohydrate, more preferably 30 wt. % or more of the carbohydrate,

and even more preferably 70 wt. % or more of the carbohydrate. Furthermore, the fast-acting intestinal regulators of the present invention in the form of a medical enteral nutrition or fluid diet may be set to have, for example, 0.1 to 3 kcal/mL, preferably 0.3 to 2.5 kcal/mL, and more preferably 0.5 to 2 kcal/mL.

5 All prior art references cited herein are incorporated by reference into the present specification.

Examples

10 Herein below, the present invention will be specifically described with reference to Examples, but it is not to be construed as being limited thereto.

[Example 1]

(1) Subjects

15 Seventy-six Thai women of ages 18 to 49 who have mild constipation (slow bowel movement or irregular bowel movement) were examined. The characteristics of the subjects are shown in Table 1 (the numerical values are mean $\pm$ standard deviation).

[Table 1]

	Total	Ages 18-29	Ages 30-39	Ages 40-49
Number of subjects	74	34	27	13
Age	31.88 $\pm$ 7.25	25.62 $\pm$ 2.35	34.19 $\pm$ 3.16	43.46 $\pm$ 3.84
Weight (kg)	55.39 $\pm$ 10.63	56.13 $\pm$ 12.67	54.57 $\pm$ 9.10	55.16 $\pm$ 8.01
Height (cm)	157.56 $\pm$ 5.96	160.12 $\pm$ 5.87	155.85 $\pm$ 5.04	155.54 $\pm$ 6.09
BMI (kg/m ²)	22.22 $\pm$ 3.77	21.85 $\pm$ 4.52	22.41 $\pm$ 3.05	22.80 $\pm$ 3.04

20 (2) Test diet

One and a half grams / package of B. G. S. powder (a composition containing Profec, dextrin, and glucose) was used as a test diet. Profec is a composition produced by fermenting whey using *Propionibacterium freudenreichii* ET-3 (propionic acid bacterial strain ET-3) and then sterilizing it. One package of B. G. S. powder (1.5 g) contained 6.5 μ g or more to 6.6 μ g
 25 or more of DHNA (1,4-dihydroxy-2-naphthoic acid).

(3) Examination schedule

The subjects took one package of the test diet (B. G. S. powder) per day at any time of the day. The first two weeks from the start of the examination (Week 1 and Week 2) was the
 30 period before intake (pre-intake period) when the subjects did not take the test diet, and the subsequent two weeks (Week 3 and Week 4) was the period during intake (intake period) when

the subjects took the test diet, and the following two weeks (Week 5 and Week 6) was the period after intake (post-intake period) when the subjects did not take the test diet.

(4) Examination method

- 5 Using a specified questionnaire sheet, "stool frequency", "degree of difficulty in defecation", "time taken for defecation", and "degree of satisfaction of defecation" before intake / during intake / after intake of the "B. G. S. powder" were investigated once every week.

(5) Restricted matters

- 10 During the examination, yogurt intake, alcohol consumption, and intestinal treatments were prohibited.

(6) Investigation results

(6-1) Change in stool frequency (stool count and stool amount)

- 15 The results of assessing the change in stool frequency (stool count and stool amount) are shown in Figs. 1, 2, and 3. According to Fig. 1, during the "intake period" when the subjects were taking the test diet, the "stool count" increased greatly. During the "post-intake period" when the subjects no longer took the test diet, the "stool count" tended to decrease in comparison to the "intake period", but "stool frequency" was maintained at a significantly high level in
20 comparison to the "pre-intake period" when the subjects were not taking the test diet.

- Furthermore, according to Figs. 2 and 3, in only one day from the start of test diet intake (W3-1), both the daily stool count (Fig. 2) and stool amount (Fig. 3) increased significantly in comparison to both the mean value for the "pre-intake period" (Week 1 and Week 2) and the mean value for the week before intake (Week 2). A further remarkable increase was observed
25 on the second day after intake of the test diet (W3-2), and such high levels were maintained throughout the intake period.

- These results showed that intake of a fast-acting intestinal regulator of the present invention expresses effects of increasing stool count and stool amount (intestine-regulating effects) in a short period of time, and that the intestine-regulating effects accompanying this
30 change is persistent.

(6-2) Change of difficulty in defecation

- Results of assessing the difficulty in defecation are shown in Fig. 4. During the "intake period", "difficulty in defecation" decreased immediately after intake of the test diet, and the
35 proportion of the response "no problem" increased. During the "post-intake period", "difficulty in defecation" tended to increase in comparison to the "intake period", but the proportion of the

response "no problem" was maintained at a significantly high level in comparison to the "pre-intake period".

These results showed that intake of a fast-acting intestinal regulator of the present invention expresses effects of improving difficulty in defecation (intestine-regulating effects) in a short period of time, that the intestine-regulating effects accompanying this change is persistent, and that there is little physical burden.

(6-3) Change in time taken for defecation

Results of assessing the time taken for defecation are shown in Fig. 5. During the "intake period", the proportion of the response "less than five minutes" greatly increased for the "time taken for defecation". During the "post-intake period", the proportion of the response "less than five minutes" tended to decrease somewhat in comparison to the "intake period", but the proportion of the response "less than five minutes" was maintained at a significantly high level in comparison to the "pre-intake period".

(6-4) Change in sensation during defecation

Results of assessing the sensation during defecation are shown in Fig. 6. During the "intake period", the frequency of abdominal pain and such decreased, and the proportion of the response "normal" greatly increased for the "sensation during defecation". During the "post-intake period", the proportion of the response "normal" tended to decrease in comparison to the "intake period", but the proportion of the response "normal" was maintained at a significantly high level in comparison to the "pre-intake period".

These results showed that intake of a fast-acting intestinal regulator of the present invention expresses effects of improving time taken for defecation and sensation during defecation (intestine-regulating effects) in a short period of time, that the intestine-regulating effects accompanying this change is persistent, and that there is little physical burden.

(6-5) Change in satisfaction of defecation

Results of assessing the satisfaction for stool frequency are shown in Fig. 7, results of assessing the satisfaction for time taken for defecation are shown in Fig. 8, results of assessing the satisfaction for stool properties are shown in Fig. 9, and results of assessing the satisfaction for stool habit are shown in Fig. 10. During the "intake period", the proportion of the responses "very satisfied" and "satisfied" greatly increased for all of stool frequency, time taken for defecation, and stool properties, and the proportion of the responses "very satisfied" and "satisfied" were maintained at significantly high levels during the "post-intake period".

These results showed that intake of a fast-acting intestinal regulator of the present

invention expresses effects of improving satisfaction of defecation (intestine-regulating effects) in a short period of time, that the intestine-regulating effects accompanying this change is persistent, and that there is little physical burden.

5 [Example 2]

(1) Subjects

One hundred and twenty eight Japanese women of ages 18 to 64 whose defecation count is approximately four times or less per week were examined.

10 (2) Test diet

Seven grams of "Amino collagen Profec" (manufactured by Meiji Co., Ltd.) was used as a test diet. "Amino collagen Profec" is composed of fish collagen peptide (gelatin), maltodextrin, fermented whey product (derived from milk), vegetable oil and fat, vitamin C, glucosamine, arginine, thickener (gum Arabic), and a flavor, and 7 g of "Amino collagen Profec" contains 6.6 μ g or more of DHNA derived from fermented whey product.

(3) Examination schedule

The subjects took the test diet for 25 days at 7 g/day at any time of the day. Regarding the days after intake, the initial day of intake was defined as "Day 0".

20 (4) Examination method

After taking the test diet, the number of days after intake for which intestine-regulating effects were felt was investigated by an interview survey.

25 (5) Examination results

The distribution of days after intake when the subjects felt the intestine-regulating effects are shown in Fig. 11 and Table 2. The day when intestine-regulating effects were initially felt varied from immediately after intake to Day 24 after intake, but the largest number of subjects felt the intestine-regulating effects on Day 0 after intake, the second largest was Day 2, and the next largest was Day 3. The cumulative proportions of subjects who felt the intestine-regulating effects as indicated in Fig. 11 and Table 2 show that half or more (approximately 54%) of the subjects felt the intestine-regulating effects by Day 4 after intake, approximately 72% by Day 6 after intake, and 80% or more (approximately 82%) of the subjects felt the intestine-regulating effects by Day 7 after intake. All subjects felt the intestine-regulating effects by Day 24 after intake, and the mean of the number of days taken to initially feel the intestine-regulating effects was approximately 4.9 days.

[Table 2]

Days after intake (day)	Number of individuals (people)	Cumulative proportion (%)
0	22	17.19
1	5	21.09
2	18	35.16
3	14	46.09
4	10	53.91
5	11	62.50
6	12	71.88
7	13	82.03
8	3	84.38
9	1	85.16
10	11	93.75
11	1	94.53
12	0	94.53
13	0	94.53
14	0	94.53
15	1	95.31
16	1	96.09
17	2	97.66
18	0	97.66
19	0	97.66
20	1	98.44
21	1	99.22
22	0	99.22
23	0	99.22
24	1	100.00

5 Industrial Applicability

The fast-acting intestinal regulators comprising a culture of propionic acid bacteria as active ingredient, which are provided by the present invention can exhibit intestine-regulating effects (particularly bowel movement-improving effects) in a short period of time when they are

taken orally. The fast-acting intestinal regulators of the present invention are composed of components proven to be safe and have superior taste properties from a long history of consumption; therefore, they are of little physical burden and can be taken for an extended period of time.

CLAIMS

1. Use of an intestinal regulator comprising a collagen peptide and a culture of propionic acid bacteria or a collagen peptide and DHNA in the manufacture of a medicament for improving constipation in patients of ages 18 to 64,

wherein the propionic acid bacteria is selected from the group consisting of *Propionibacterium freudenreichii*, *Propionibacterium acidipropionici*, and *Propionibacterium jensenii*,

wherein improvement of constipation is obtained within 7 days of administration of the medicament and maintained for at least two weeks from after stopping administration of the medicament, and

wherein the content of DHNA in the medicament is 5 µg to 100 µg per day or the content of the culture of propionic acid bacteria in the medicament is 0.001 to 20wt%.

2. Use of an intestinal regulator comprising a collagen peptide and a culture of propionic acid bacteria or a collagen peptide and DHNA in the manufacture of a medicament for improving mild constipation in patients of ages 18 to 64,

wherein the propionic acid bacteria is selected from the group consisting of *Propionibacterium freudenreichii*, *Propionibacterium acidipropionici*, and *Propionibacterium jensenii*,

wherein improvement of mild constipation is obtained within 7 days of administration of the medicament and maintained for at least two weeks from after stopping administration of the medicament, and

wherein the content of DHNA in the medicament is 5 µg to 100 µg per day or the content of the culture of propionic acid bacteria in the medicament is 0.001 to 20wt%.

3. The use of claim 1 or 2, wherein the propionic acid bacteria is *Propionibacterium freudenreichii*.

4. The use of any one of claims 1 to 3, wherein improvement of constipation is characterized by any one or more of increase in stool count, increase in stool amount, improvement of difficulty in defecation, shortening of time taken for defecation, improvement of sensation during defecation, improvement of stool frequency, improvement of stool properties, and improvement of stool habits.

5. The use of any one of claims 1 to 4, wherein improvement of constipation is obtained within 2 days of administration of the medicament.

6. The use of any one of claims 1 to 4, wherein improvement of constipation is obtained within 1 day of administration of the medicament.

ABSTRACT

The present invention provides fast-acting intestinal regulators containing a culture of propionic acid bacteria, DHNA, or an analog thereof, as an active ingredient, which expresses
5 effects of regulating the intestine within one day after intake, and expresses more noticeable effects of regulating the intestine within two days after intake. The present invention also provides fast-acting intestinal regulators containing a culture of propionic acid bacteria, DHNA, or an analog thereof, as an active ingredient, which maintains intestine regulating effects for two weeks after its intake.

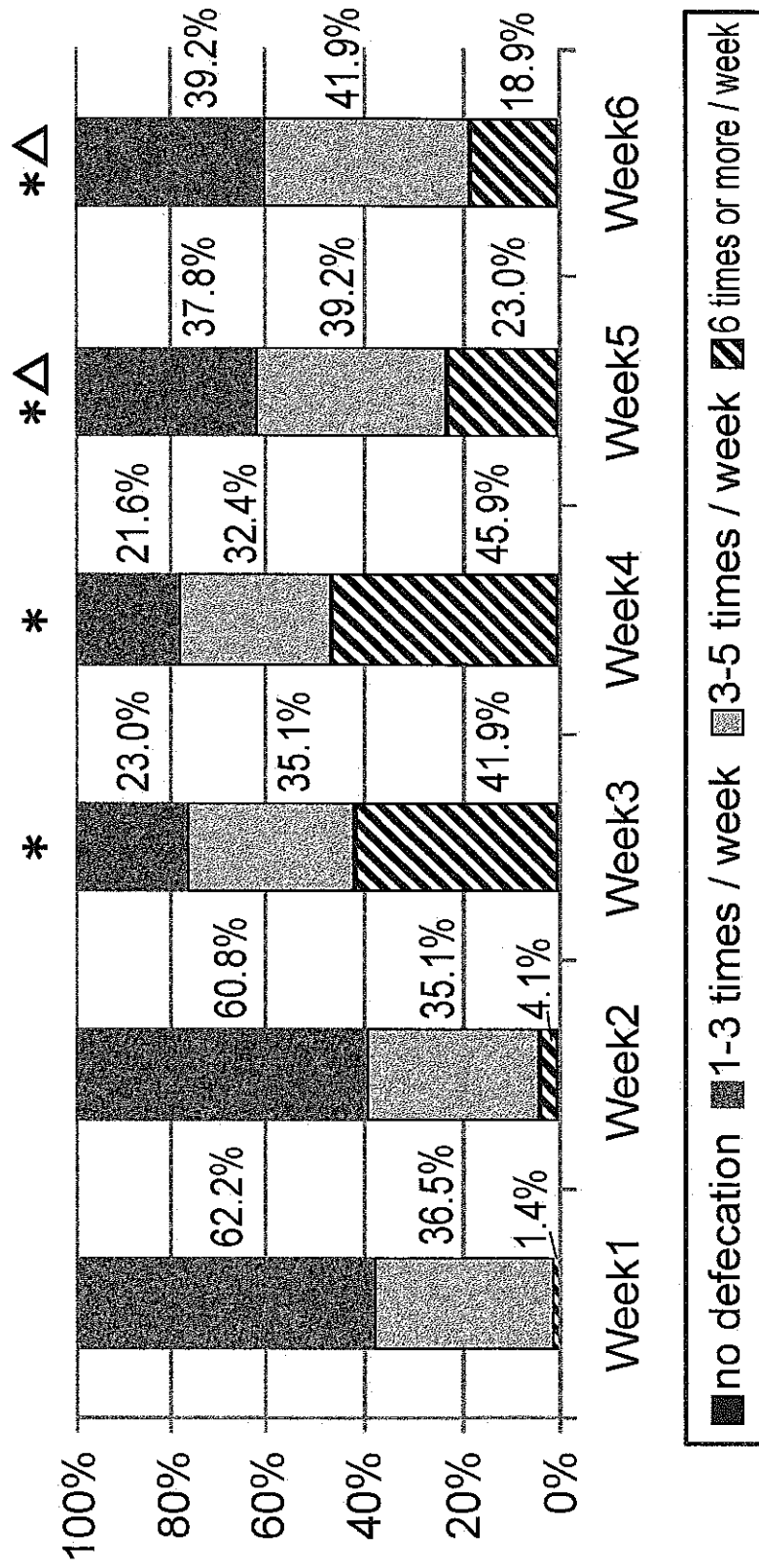


FIG. 1

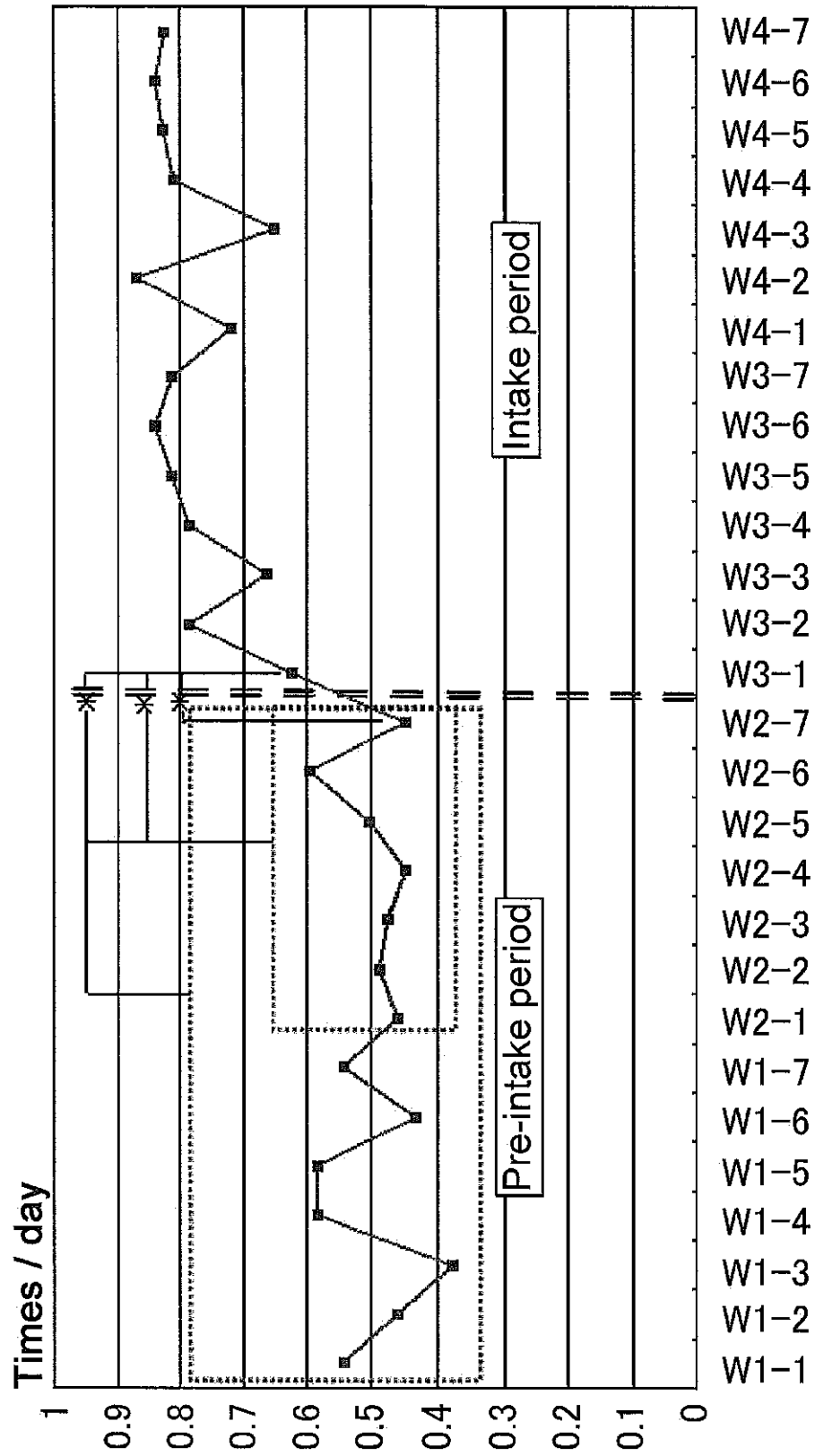


FIG. 2

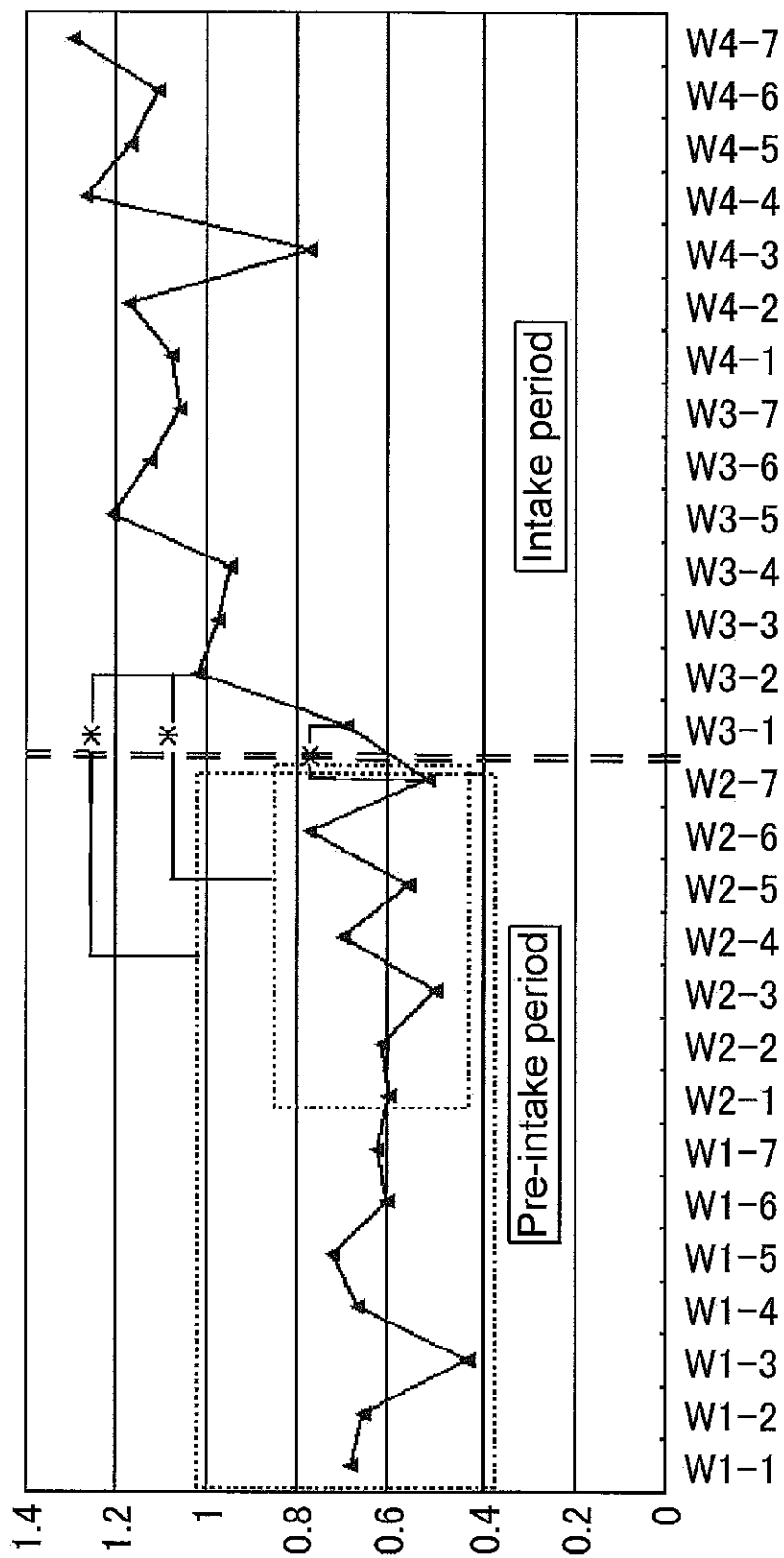


FIG. 3

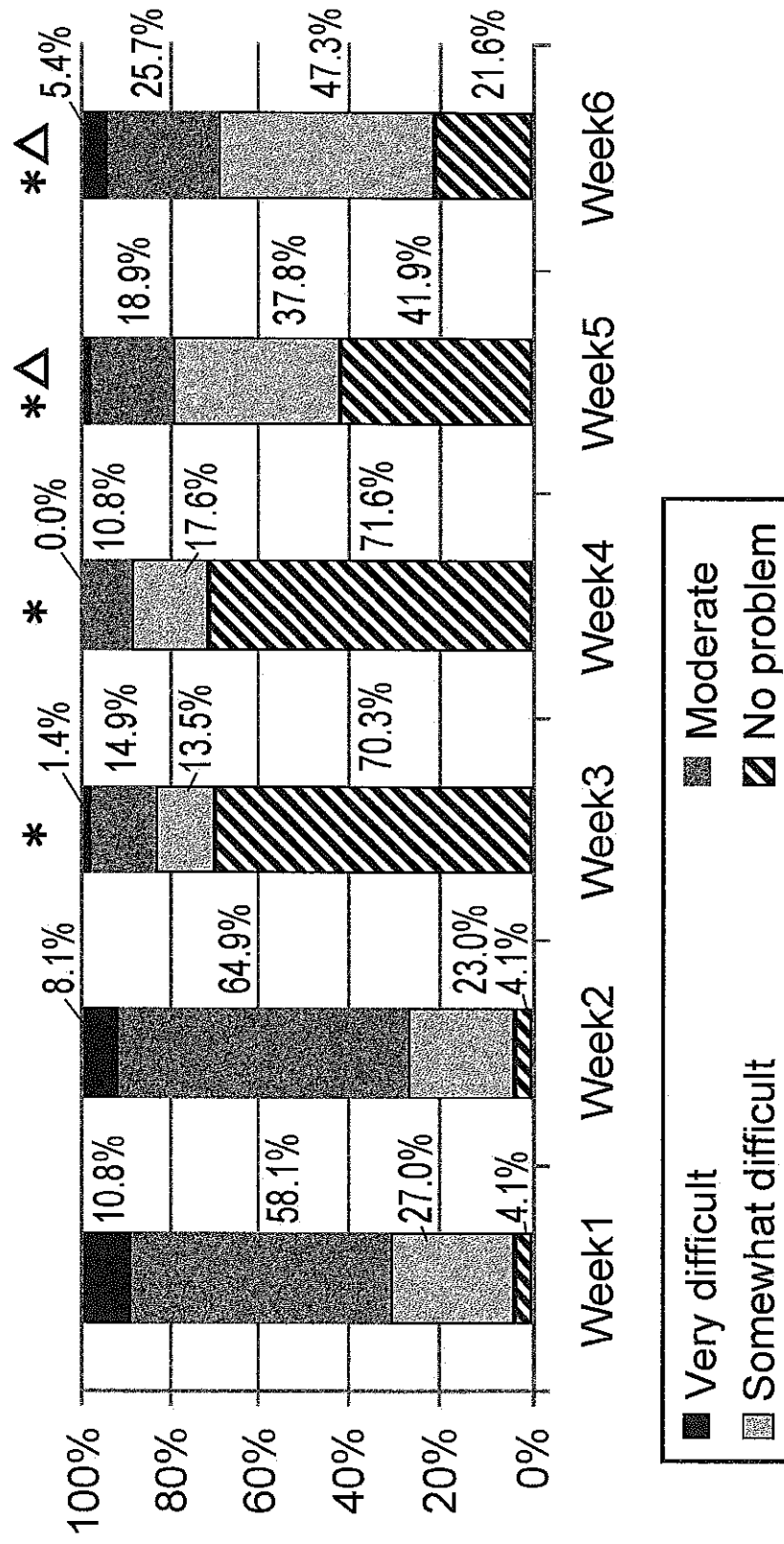


FIG. 4

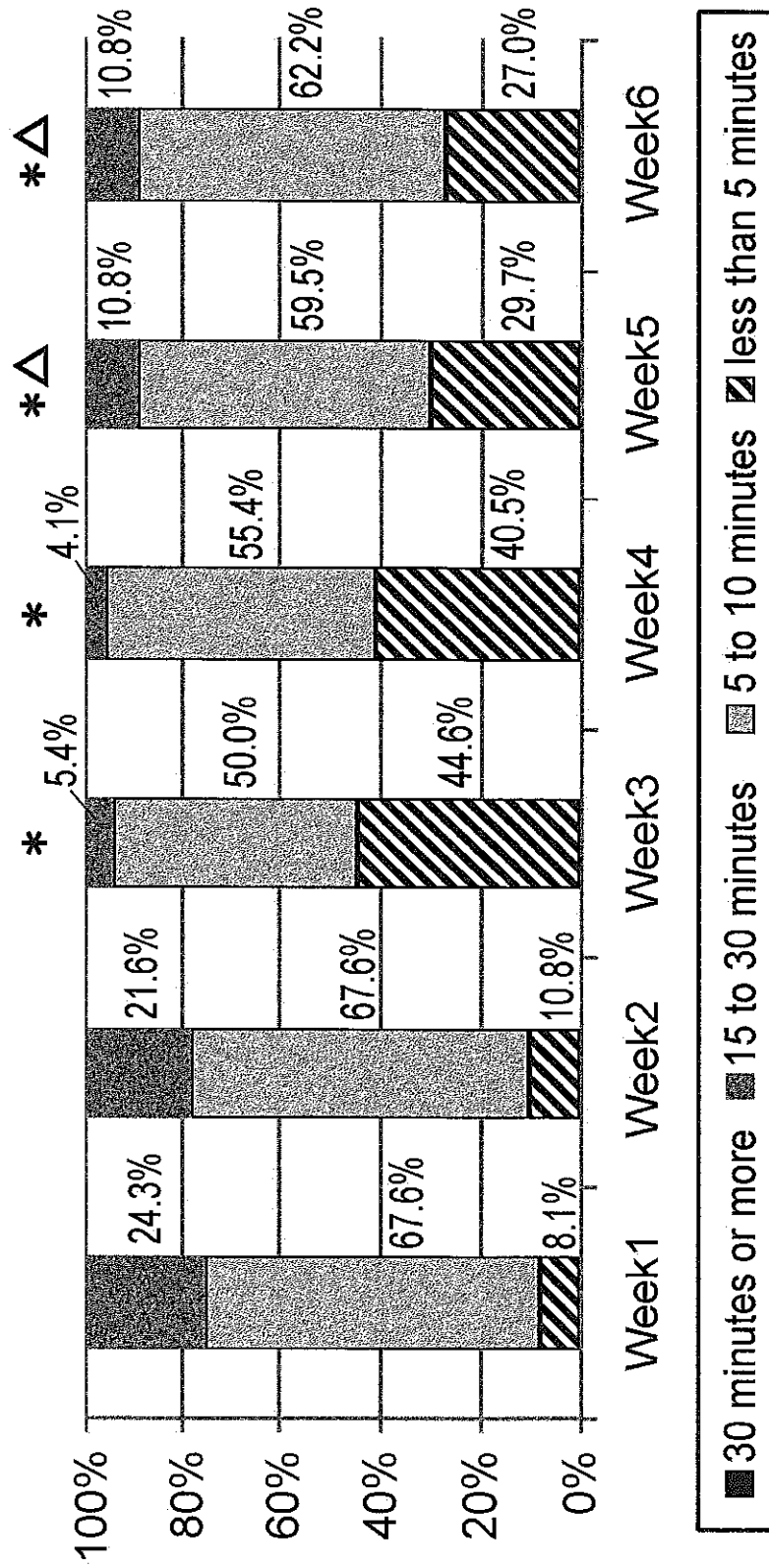


FIG. 5

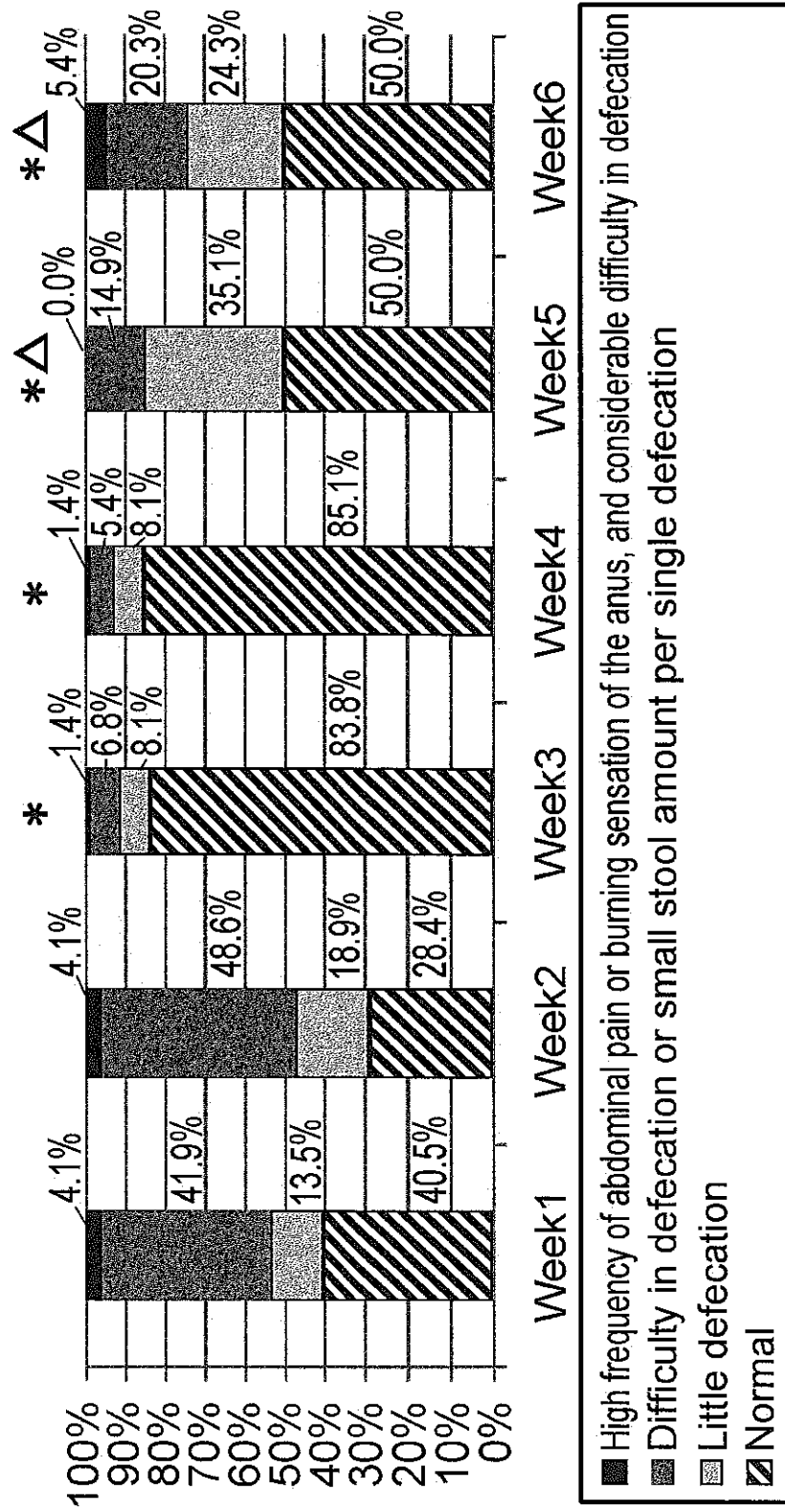


FIG. 6

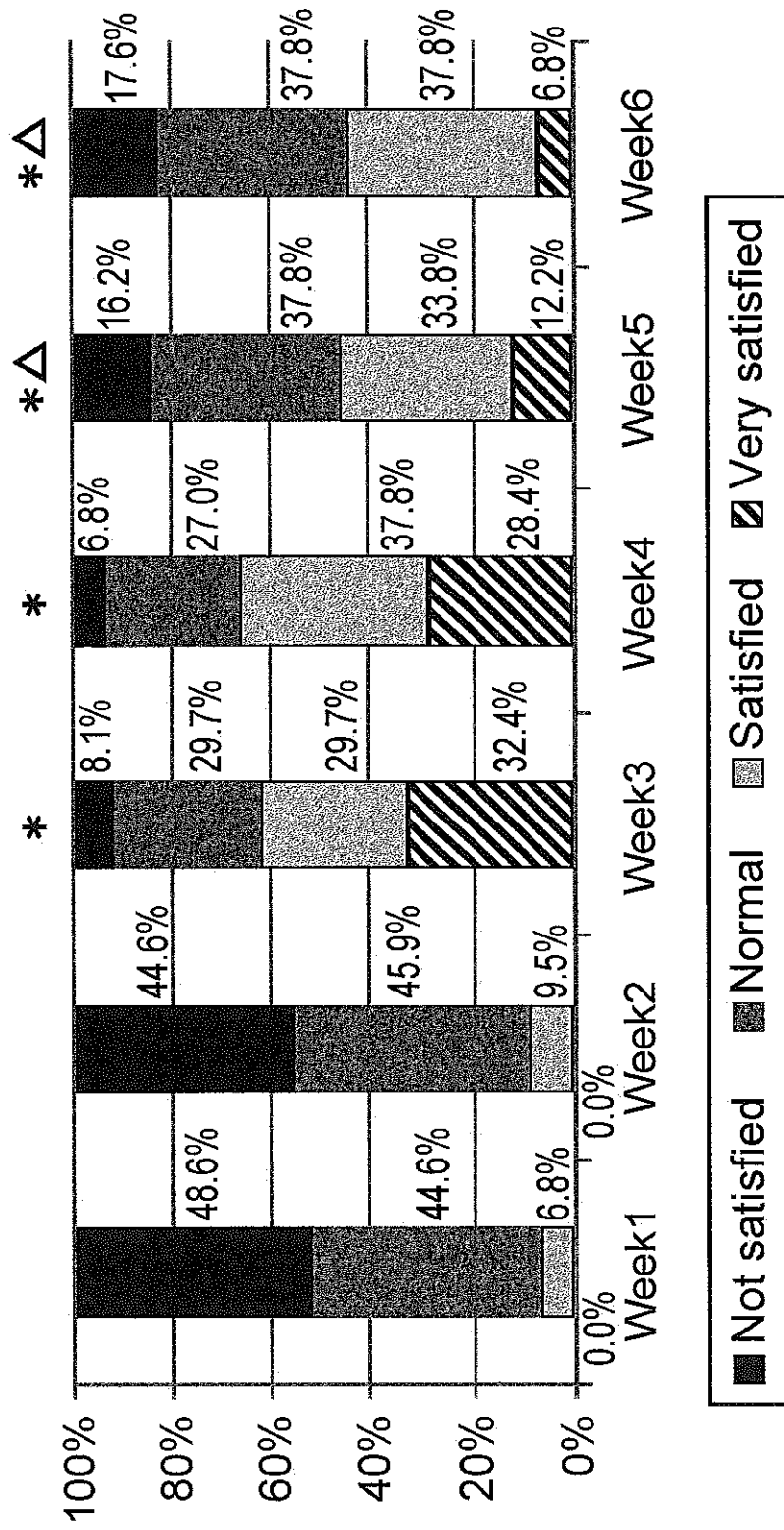


FIG. 7

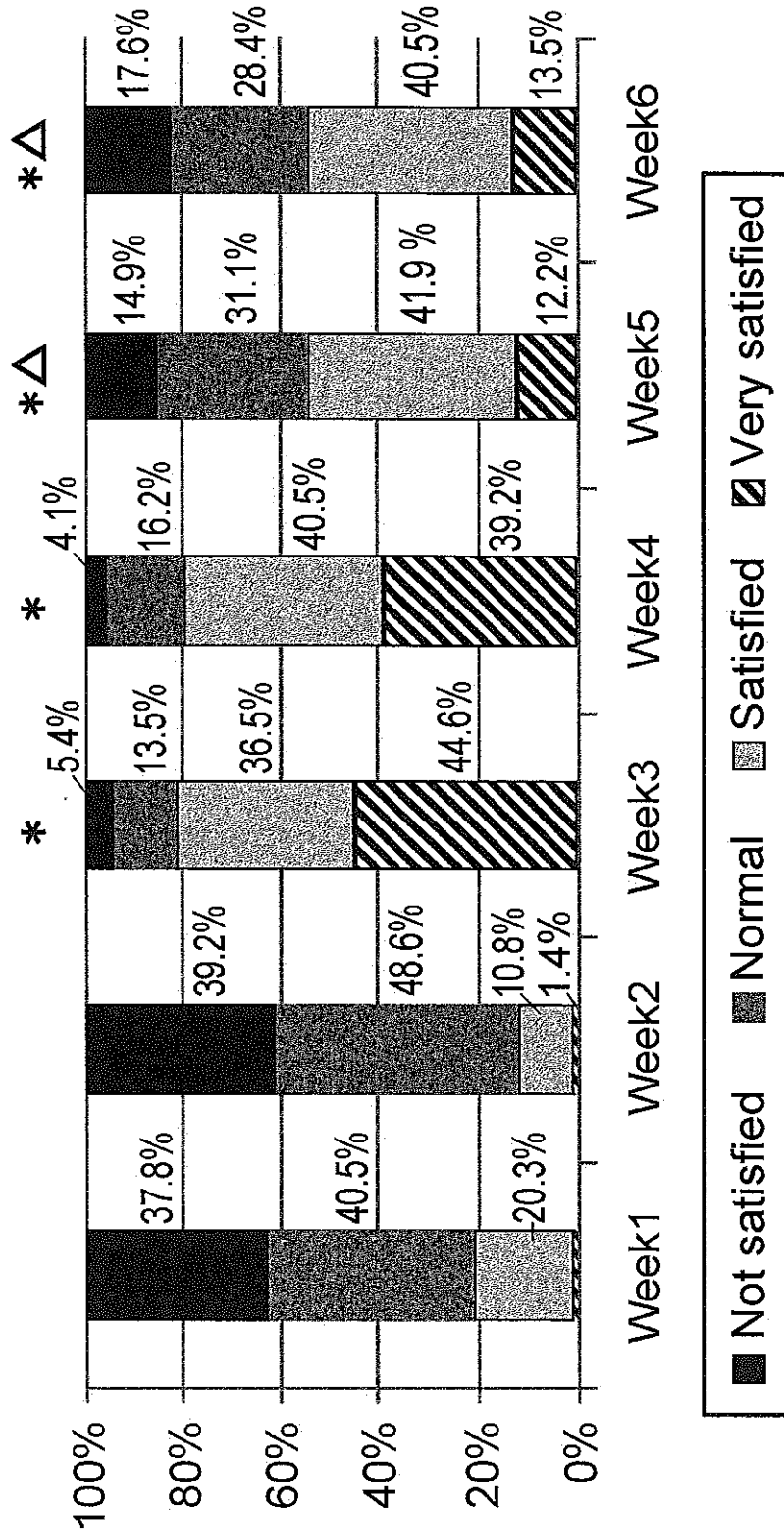


FIG. 8

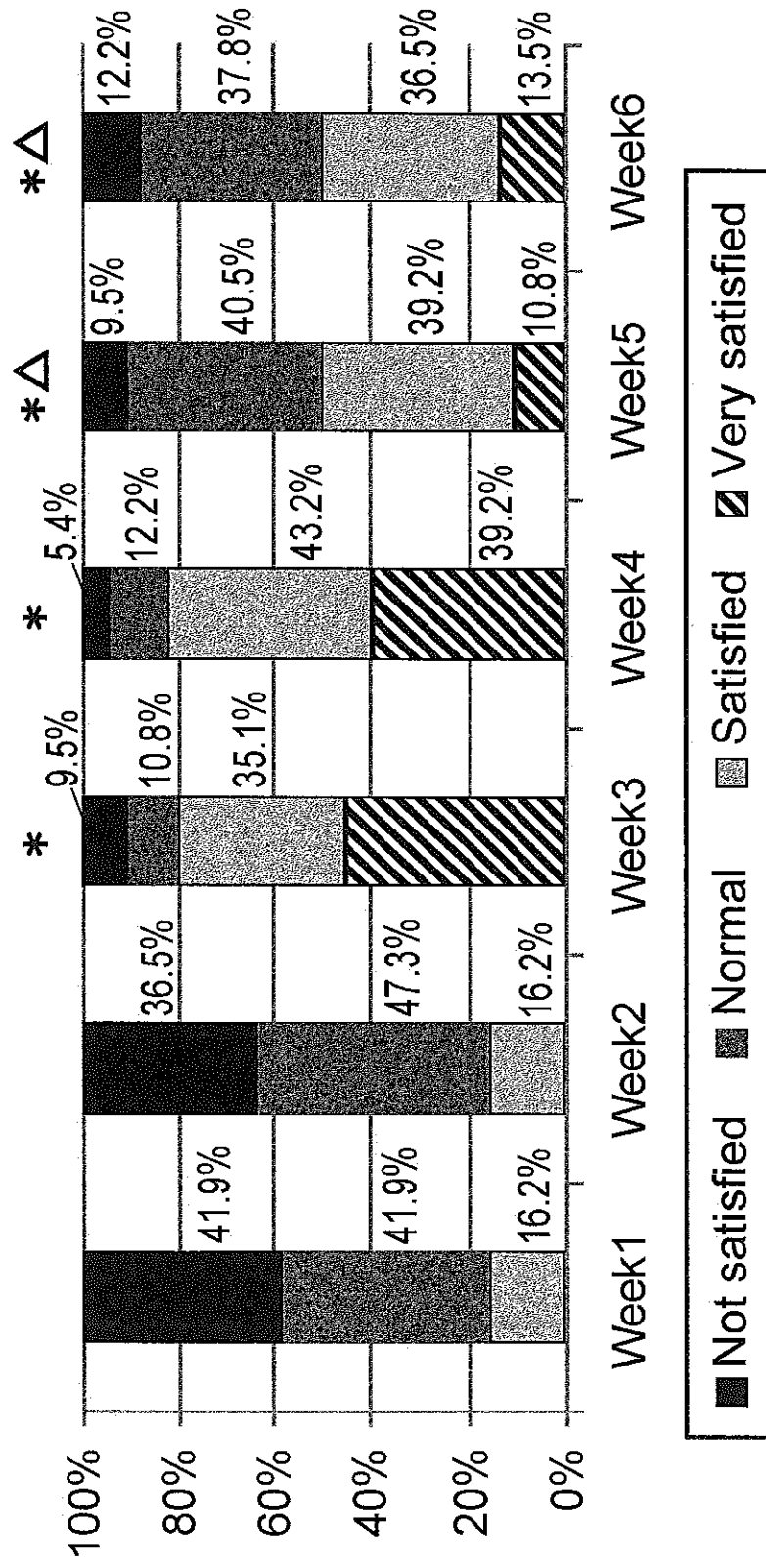


FIG. 9

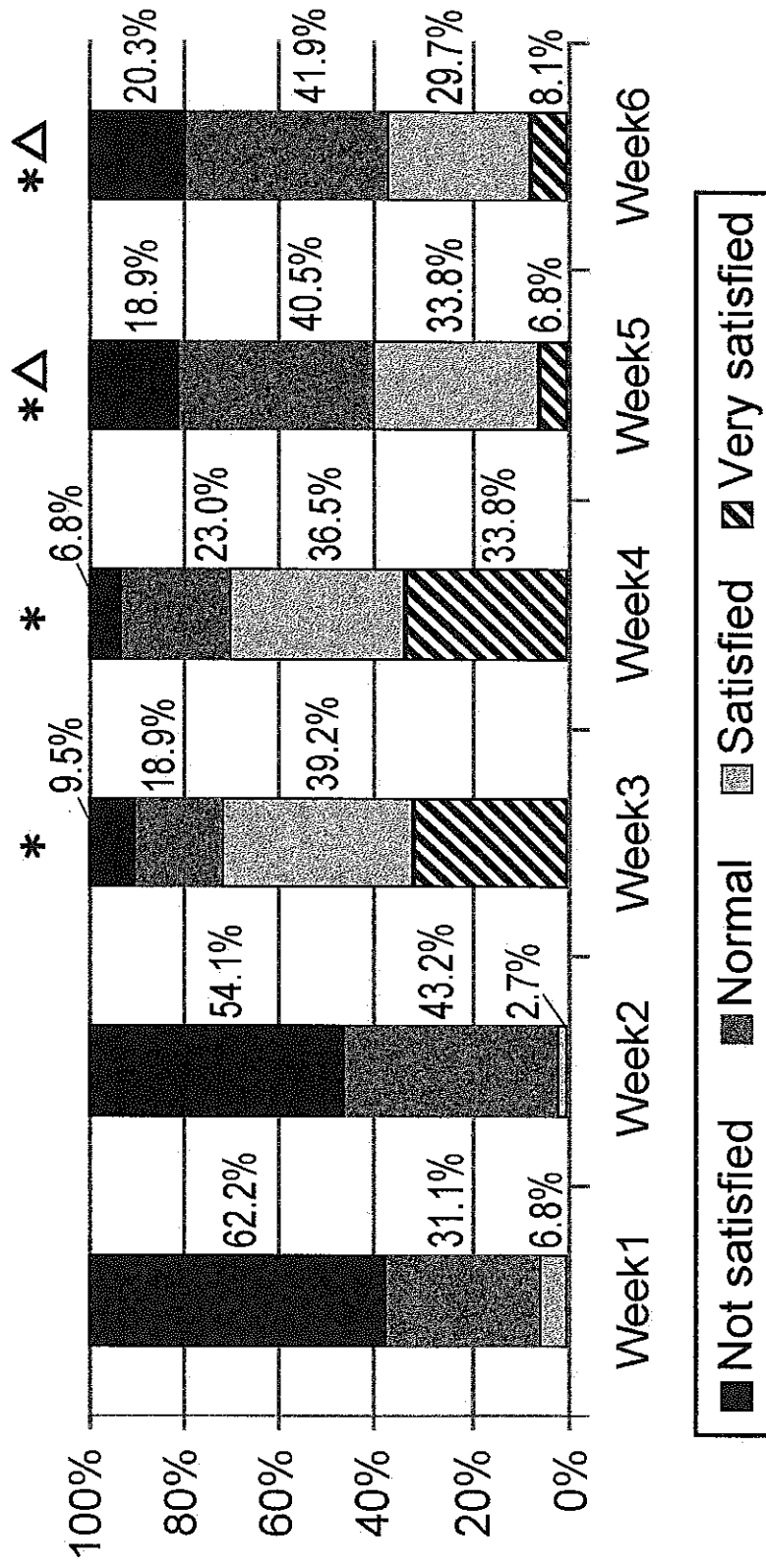


FIG. 10

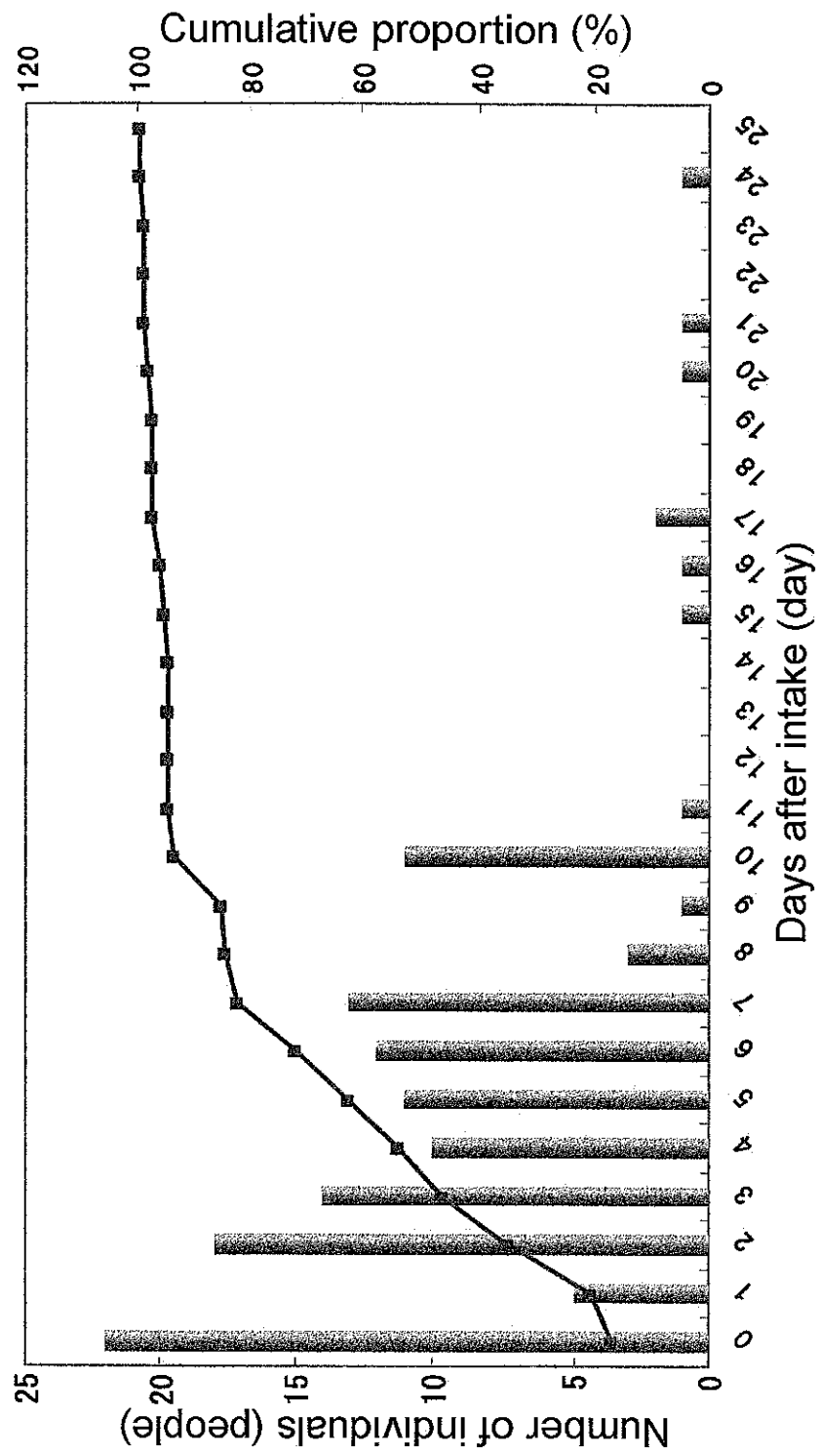


FIG. 11