# Clinical Study Protocol

## Efficacy and Safety of DWJ1319 in the Prevention of Gallstone Formation after Gastrectomy in Patient with Gastric Cancer: A Multicenter, Randomized, Double-blind, Placebo-controlled Study

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| **Protocol No.** | DW_UDCA005 |
| **Study Phase** | Phase III (Therapeutic Confirmatory Study) |
| **Protocol Version** | 2.3_ English Translation Version |
| **Effective Date** | 2016/02/23 |

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## ※ Protocol Synopsis

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|---|---|
| **Study Title** | Efficacy and Safety of DWJ1319 in the Prevention of Gallstone Formation after Gastrectomy in Patient with Gastric Cancer: A Multicenter, Randomized, Double-blind, Placebo-controlled Study |
| **Study Phase and Design** | Therapeutic Confirmatory Study (Phase III)<br>Multicenter, Randomized, Double-Blind, Placebo-controlled, Parallel study |
| **Sponsor** | Daewoong Pharmaceutical Co., Ltd.<br>12, Bongeunsa-ro 114-gil, Gangnam-gu, Seoul 135-715, Rep. of Korea |
| **Study Site** | 12 sites |
| **Coordinating Investigator** | Prof. Do-Joong Park, Department of Surgery, Seoul National University Bundang Hospital |
| **Study Objective** | 1. To assess the efficacy of DWJ1319 300 mg or DWJ1319 600 mg administered once daily for 52 weeks in the prevention of gallstone formation after gastrectomy in patients with gastric cancer compared with placebo.<br>2. To assess the safety and tolerability of DWJ1319 300 mg or DWJ1319 600 mg administered once daily for 52 weeks compared with placebo. |
| **Subject** | Patients who were diagnosed with gastric cancer and underwent gastrectomy as treatment |
| **Number of Subjects** | 138 subjects are required per group when the subjects are randomized to the placebo group, DWJ1319 300 mg group, or DWJ1319 600 mg group in a 1:1:1 ratio, and considering 20% dropout rate, a total of 519 subjects will be enrolled with 173 subjects per group. |
| **Study Period** | • Overall study period: Approximately 20 months from the approval of the protocol (subject to change depending on the status of subject enrollment.)<br>• Study period for each subject: 54 weeks<br>- Screening period: 2 weeks<br>- Treatment period: 52 weeks (12 months) |
| **Inclusion Criteria** | 1. Patients who voluntarily agree to participate in the study and sign the informed consent form<br>2. Patients at least 19 years of age at the time of informed consent<br>3. Patients who were diagnosed with gastric cancer and underwent any one of the following gastrectomies<br>1) Total gastrectomy<br>2) Distal gastrectomy<br>3) Proximal gastrectomy<br>4. Patients who underwent D1+ or D2 lymph node dissection<br>5. Patients with ECOG performance status scale ≤ 1 point (Appendix 1)<br>6. Life expectancy of at least 3 months<br>7. Patients who can be enrolled in the study within 2 weeks from gastrectomy |
| **Exclusion Criteria** | 1. Patients with cholangitis, cholecystitis, non-functional gall bladder, or biliary obstruction<br>2. History of previous cholecystectomy<br>3. Patients with gallstones observed on medical imaging (abdominal ultrasound, abdominal CT) performed at screening or during gastrectomy<br>4. Patients who underwent pylorus-preserving gastrectomy<br>5. Patients who have undergone or are currently undergoing treatment for peptic ulcer (acute gastric and duodenal ulcers), pancreatitis, colon and small intestine (Crohn's disease, etc.) within 4 weeks prior to the screening.<br>6. Patients with variceal bleeding, fulminant hepatic failure, active hepatitis, liver cirrhosis, hepatic coma or ascites, or requiring a liver transplantation<br>7. Patients with hypersensitivity to bile acid or ursodeoxycholic acid<br>8. Patients who require total parenteral nutrition for ≥ 1 week<br>9. Patients with BMI > 37 $kg/m^2$ at screening |

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|---|---|
| | 10. Patients with uncontrolled diabetes (glycosylated hemoglobin (HbA1c) level ≥ 9%)<br>11. Patients with clinically significantly abnormal values in the screening test<br>1) ALT, AST, BUN, or total bilirubin > 2.5 x the upper limit of normal<br>2) eGFR < 60 ml/min/1.73 $m^2$<br>12. Patients who require prohibited concomitant medication(s) during the study period or cannot comply with the wash-out period for prohibited concomitant medication(s)<br>13. Pregnant or breast feeding women and women of childbearing age who are not using reliable contraceptive method during the study period or do not agree to maintain contraception during the study period<br>- Methods of contraception: Use of at least two contraception methods among abstinence, subject's or his/her partner's surgical sterilization (vasectomy, etc.) or barrier methods using intrauterine device, condom, or spermicide is recommended.<br>14. Patients with history of drug or alcohol abuse within 5 years prior to study entry<br>15. Patients who were diagnosed with a cancer other than gastric cancer, basal cell or squamous epithelial skin cancer within 5 years prior to study entry<br>16. Patients with physical or mental dysfunction that participating in this study may expose them to the risks or confuse the results, or that cannot comply with the study requirements based on the judgment of the investigator.<br>17. Patients who received other investigational products within 30 days or ≥ 5 elimination half-life prior to screening, whichever is longer<br>18. Difficulty in performing the study, as judged by the investigator |
| **Investigational Product** | 1. Study drug: DWJ1319 (Ursa-D Capsule 300 mg)<br>1) Dosage form and appearance: Hard capsule of pink upper half and white lower half containing white to light yellow granules<br>2) Ingredient: Ursodeoxycholic acid 300 mg<br><br>2. Comparator: Placebo<br>1) Dosage form and appearance: Hard capsule of pink upper half and white lower half containing white to light yellow granules<br>2) Ingredient: Placebo for DWJ1319 |
| **Period and Method of Administration of Investigational Products** | Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be randomized into either the study group or the control group and orally receive the investigational product 1 capsule twice daily (morning and evening) for a whole year (52 weeks). |

**Study Method**

Subjects who meet all of the inclusion criteria and none of the exclusion criteria at screening (Visit 1) will be randomized into one of the placebo group, DWJ1319 300 mg group, or DWJ1319 600 mg group (1:1:1). For randomization, stratified randomization using the study site, the lymph node resection range, and the type of gastrectomy as the stratification factors will be performed and randomization will be performed within 2 weeks from gastrectomy. During the study period, the subjects will visit the study site at screening, randomization (Day 1) and at 3-month interval after the administration of investigational product (at 3, 6, 9, and 12 months) to undergo protocol-specified tests and procedures at each visit. However, any subject with formation of gallstone confirmed during the treatment period will terminate the study at the time of confirmation.

| Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|---|---|---|---|---|---|
| Until Week -2 | Day 1 | Month 3 ±1 week | Month 6 ±1 week | Month 9 ±1 week | Month 12 ±1 week |
| Screening | Randomization | Treatment period | | | |

**Prohibited concomitant medications**

**[Prohibited concomitant medications]**

| Medication class | Temporary (As needed) | Chronic | Restrictions |
|---|---|---|---|
| tolbutamide | Not allowed | Not allowed | Concomitant use is prohibited from 48 hours prior to Visit 1 throughout the study |
| cholestyramine colestipol | Not allowed | Not allowed | Concomitant use is prohibited from 48 hours prior to Visit 1 throughout the study |
| Medicinal charcoal, smectite<br>Antacids containing magnesium or aluminum hydroxide | Allowed | Not allowed | Concomitant use is prohibited after Visit 2 throughout the study; Temporary use is permitted if a 4-hour interval from the administration of the investigational product is maintained |
| Estrogen<br>Oral contraceptive<br>Fenofibrate, bezefibrate | Not allowed | Not allowed | Concomitant use is prohibited from 4 weeks prior to Visit 1 throughout the study |
| Octreotide | Not allowed | Not allowed | Concomitant use is prohibited from 24 hours prior to Visit 1 throughout the study |
| NSAIDs (except for the low dose aspirin) | Allowed | Not allowed | Concomitant use is prohibited from 4 weeks prior to Visit 1 throughout the study; Only the temporary use is permitted |
| Ceftriaxone | Allowed | Not allowed | Concomitant use for 1 consecutive week or more is prohibited after Visit 2 throughout the study |
| Immunosuppressant (cyclosporine, tacrolimus) | Not allowed | Not allowed | Concomitant use from 1 week before Visit 1 throughout the study is prohibited |

<table>
<tr><td>Prohibited concomitant medications (continued)</td><td>
[Prohibited concomitant medications] (continued)
<table>
<tr><th>Medication class</th><th>Temporary (As needed)</th><th>Chronic</th><th>Restrictions</th></tr>
<tr><td>Parenteral nutrition</td><td>Allowed</td><td>Not allowed</td><td>Concomitant use for 1 consecutive week or more is prohibited after Visit 2 throughout the study</td></tr>
<tr><td>Bile salt extract or choleretics</td><td>Not allowed</td><td>Not allowed</td><td>Concomitant use is prohibited from 4 weeks prior to Visit 1 throughout the study; Temporary use of UDCA ≤ 25 mg/day is allowed, but the overall treatment period cannot exceed 1 month.</td></tr>
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<tr><td>Efficacy Assessment</td><td>
1. Primary Endpoint: Proportion of subjects with gallstone formation within 12 months after gastrectomy according to an assessment by an external investigator<br><br>
2. Secondary Endpoints<br>
1) Proportion of subjects developing gallstone within 3, 6, 9, and 12 months from gastrectomy<br>
2) Proportion of subjects developing gallstone within 3, 6, and 9 months from gastrectomy as assessed by the external investigator<br>
3) Proportion of subjects developing biliary sludge within 3, 6, 9, and 12 months from gastrectomy<br>
4) Time to gallstone formation<br><br>
3. Other Endpoints<br>
1) Change in the bile reflux symptoms from baseline at 3, 6, 9, and 12 months<br>
2) Proportion of subjects who experience bile reflux on the upper gastrointestinal endoscopy at 3 and 12 months<br>
3) Proportion of subjects with significant AST and ALT abnormalities at 6 and 12 months
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<tr><td>Safety Assessment</td><td>Adverse events, laboratory tests (hematology/blood chemistry/urinalysis), physical examination, vital signs</td></tr>
<tr><td>Statistical Analysis Method</td><td>
Unless otherwise specified, in principle, this study will perform a two-sided test by setting the significance level for the statistical tests at 0.05.<br><br>
1. Efficacy Assessment<br>
1) Primary Efficacy Endpoint<br>
For the superiority of DWJ1319 over placebo on the incidence of gallstone formation, the sequential multiple testing will be performed for each treatment group according to the fixed sequence method.<br>
• Step 1: Superiority testing for DWJ1319 600 mg compared with placebo (5% significance level)<br>
• Step 2: Superiority testing for DWJ1319 300 mg compared with placebo (5% significance level)<br><br>
The step 2 test can be performed only if the result of step 1 test is statistically significant, and the conclusions about the superiority of DWJ1319 over placebo will be drawn based on the test result from each step. If the result of step 1 test is not statistically significant, the step 2 test will not be performed, and it will be concluded that both treatment groups of DWJ1319 have failed to demonstrate the superiority over placebo.<br><br>
The test in each step will use the logistic regression model with the lymph node resection range and the type of gastrectomy as covariates and present the frequency and proportion along with confidence intervals of subjects who have
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formed gallstone within 12 months by treatment group.

2) Secondary and Other Efficacy Endpoints
With regard to the onset rate of gallstones within each time point after gastrectomy, frequency and proportion, and the 95% confidence intervals for each of the assessments by the external investigator was provided. The difference between each treatment group of DWJ1319 versus placebo is analyzed using a logistic regression model with the lymph node resection range and the type of gastrectomy as covariates.

With regard to the categorical data such as the onset rates of the biliary sludge and biliary reflux within each time point after gastrectomy and significant abnormal rates of AST, ALT values at each time point, frequency and proportion, and the 95% confidence intervals are provided. The difference between each treatment group of DWJ1319 versus placebo is analyzed using a logistic regression model with the lymph node resection range and the type of gastrectomy as covariates.

Data on the time it took for gallstones to be formed is analyzed using the cox proportional hazards regression model with the lymph node resection range and gastrectomy as prognostic factors.

For scores of questionnaire on bile reflux symptoms, the score of each typical symptom (upper abdominal pain, heartburn, nausea) and the total score of symptoms will be presented in three categories which are frequency, intensity, and the level of distress. For the changes in the score of bile reflux symptom, the difference in the three categories between the DWJ1319 treatment groups compared with placebo is analyzed using analysis of covariance with the lymph node resection range and the type of gastrectomy as the covariates.

**2. Safety Assessment**
The result of the last assessment performed prior to the initial administration of the investigational product will be used as the baseline for the safety endpoint.

1) Adverse Events
Descriptive statistics (number of subjects, incidence, and number of cases) will be presented by treatment group for the treatment emergent adverse event (TEAE), adverse drug reaction (ADR), and serious adverse event (SAE), and the two-sided 95% confidence intervals for the incidence will also be presented. The differences in proportions between the treatment groups will be compared using the chi-square test or Fisher’s exact test.

2) Laboratory Tests and Vital Signs
Descriptive statistics (mean, standard deviation, minimum, median, and maximum) will be presented by treatment group for the measurements at each time point and the change from baseline after the administration of the investigational product, and the frequency and proportion will be presented for categorical measurement results. The treatment groups will be compared by ANOVA or a Kruskal–Wallis test for continuous data, and by the chi-square test or Fisher’s exact test for categorical data.

For the laboratory tests, the proportion of subjects who are normal or not clinically significant abnormal before the administration of the investigational product but changed to clinically significant abnormal after the administration will be analyzed using the chi-square test or Fisher's exact test.

3) Physical Examination
For each item of physical examination, the frequency and proportion of normal/abnormal subjects will be provided.

## ※ Schedule of Study Activities

| | Screening | Baseline | Treatment | | | |
|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 / Early Termination[1] |
| Duration | From Week -2 Day -1 | Day 1 | Month 3 (±1 week) | Month 6 (±1 week) | Month 9 (±1 week) | Month 12 (±1 week) |
| Informed consent[2] | ○ | | | | | |
| Demographic survey | ○ | | ○[3] | ○[3] | ○[3] | ○[3] |
| Medical/surgical history | ○ | ○ | | | | |
| Physical examination | ○ | | | ○ | | ○ |
| Vital signs | ○ | ○ | ○ | ○ | ○ | ○ |
| Inclusion/exclusion criteria | ○ | ○ | | | | |
| Randomization | | ○ | | | | |
| Abdominal ultrasound and reading[4] | ○[5] | | ○ | ○ | ○ | ○ |
| Abdominal CT scan | ○[5] | | | ○ | | ○ |
| Assessment of bile reflux symptoms | | ○ | ○ | ○ | ○ | ○ |
| Upper gastrointestinal endoscopy | | | ○ | | | ○ |
| Laboratory tests | ○[6] | | ○[7] | ○ | ○[7] | ○ |
| Pregnancy test[8] | ○ | | | | | |
| Prescription of investigational products | | ○ | ○ | ○ | ○ | |
| Treatment compliance | | | ○ | ○ | ○ | ○ |
| Adverse events | | | ○ | ○ | ○ | ○ |
| Prior/concomitant medications[9] | ○ | ○ | ○ | ○ | ○ | ○ |

1) For a dropout or early termination, the procedures for Visit 6 will be performed.
2) The informed consent form will be obtained in writing prior to study initiation after explaining the objectives and details of the study to the subjects. The informed consent should be obtained prior to any study procedures.
3) At the screening visit, the demographic information (subject initials, gender, date of birth, smoking status and alcohol use, weight, height, BMI, etc.) will be collected. Thereafter, only the weight will be measured at each visit.
4) Will be measured in a fasted state (including the investigational product) on the day of visit. If not in a fasted stated on the day of visit, the test will be conducted by re-visiting during the imaging test window (regular visit ± 2 weeks). A subject with gallstone formation confirmed during the study period will terminate the study at the time of confirmation.
5) If there is a recent radiology result (within 6 weeks before screening), the result can be used as a screening test.
6) Abdominal CT scan and upper gastrointestinal endoscopy (once in 3 months or 12 months) are periodic examinations that are usually performed in connection with gastrectomy. If there is a result for the corresponding examination, result of the periodic examination shall be collected and utilized.
7) If the test result performed during the screening test does not meet the exclusion criteria, re-testing may be conducted only once.
8) At Visits 3 and 5, Liver function tests (ALT, AST, ALP, γ-GTP, and total bilirubin) among laboratory tests will be performed.
9) Urine HCG test will be performed only in women of childbearing age and the result should be confirmed prior to the administration of the investigational product.

10) Any drug that has been administered from 4 weeks before the screening visit throughout the study or is currently administered should be recorded.

## ※ Definition of Terminologies and Abbreviations

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| AJCC | American Joint Committee on Cancer |
| ALP | Alkaline Phosphatase |
| ALT(=SGPT) | Alanine Transaminase (aminotransferase) |
| ANOVA | Analysis of Variance |
| AST(=SGOT) | Aspartate Transaminase (aminotransferase) |
| BUN | Blood Urine Nitrogen |
| CT | Computed tomography |
| ECOG | Eastern Cooperative Oncology Group |
| eGFR | Estimated Glomerular Filtration Rate |
| FAS | Full Analysis Set |
| γ-GTP(=γ-GT) | Gamma-glutamyl transpeptidase (Gamma-glutamyl transferase) |
| GCP | Good clinical practice |
| Hb | Hemoglobin |
| Hct | Hematocrit |
| ICH | International Conference on Harmonization |
| IRB | Institutional Review Board |
| IWRS | Interactive web response system |
| MedDRA | Medical dictionary for regulatory activities |
| NSAIDs | Non-Steroidal Anti-Inflammatory Drugs |
| PP | Per Protocol |
| PT | Preferred Term |
| RBC | Red blood cell |
| SAE | Serious adverse event |
| SOC | System Organ Class |
| TEAE | Treatment Emergent Adverse Event |
| UDCA | Ursodeoxycholic acid |
| WBC | White blood cell |

# 1. Study Title and Phase

## 1.1. Title

Efficacy and safety of DWJ1319 in the prevention of gallstone formation after gastrectomy in patient with gastric cancer: A multicenter, randomized, double-blind, placebo-controlled study

## 1.2. Phase

Therapeutic confirmatory study (Phase III study)

# 2. Name and Address of Study Sites

## 2.1. Study Sites

Appendix 1. List of Study Sites and Principal Investigators

# 3. Managers, Staff, and Managing Pharmacists of Study

## 3.1. Coordinating Investigator

Prof. Do-Joong Park, Department of Surgery, Seoul National University Bundang Hospital

## 3.2. Principal Investigators and Sub-investigators

Appendix 1. List of Study Sites and Principal Investigators
Appendix 2. List of Sub-investigators

## 3.3. Managing Pharmacists

Appendix 3. List of Managing Pharmacists

# 4. Name and Address of Sponsor

## 4.1. Sponsor

Name: Daewoong Pharmaceutical Co., Ltd.
Address: 114gil 12 Bongeunsa-ro, Gangnam-gu, Seoul

## 4.2. Contract Research Organization (CRO)

Name: LSK Global Pharma Services Co., Ltd.
Address: 16th Fl., Yeongak Tower of the Korea University, 97 Toegye-ro, Jung-gu, Seoul

## 4.3. Study Advisor

Professor Lee, Sang-Hyeop, Department of Internal Medicine, Seoul National University Hospital

# 5. Objective and Background of Study

## 5.1. Study Objective

1) To assess the efficacy of DWJ1319 300 mg or DWJ1319 600 mg administered once daily for 52 weeks in the prevention of gallstone formation after gastrectomy in patients with gastric cancer compared with placebo.
2) To assess the safety and tolerability of DWJ1319 300 mg or DWJ1319 600 mg administered once daily for 52 weeks compared with placebo.

## 5.2. Study Background

As domestic incidences of cancer continue to rise, gastric cancer is the second most common cancer accounting for 17.2% of total cancer incidences. In particular, it is the most common type of

cancer in men, occurring more frequently than prostate cancer and colon cancer.[1] Furthermore, due to early screening and the development of treatment techniques, the 5-year survival rate of patients with gastric cancer has been increasing every year. Therefore, there is a trending decrease in complications for these patients due to the treatment, and a growing interest in improving their quality of life.

Currently, surgical treatment, chemotherapy, and radiation therapy are performed to treat gastric cancer. To date, surgical treatment is known to be the most fundamental and effective method for increasing the survival rate. Thus, the standard treatment for gastric cancer is surgery if a radical resection is possible.[2] However, due to various causes such as anatomical changes after gastrectomy, major complications have been reported including alkaline reflux gastritis, reflux esophagitis, iron deficiency anemia, vitamin $B_{12}$ deficiency, metabolic bone disease and cholelithiasis.[3]

The proportion of patients with gallstone formation has been reported to be approximately 13%-17% within 1 year and 20% within 5 years after gastrectomy, and this is about 10% higher than the prevalence of gallstones in the general population (2.0% in Korea and 3.2% in Japan).[4]-[8] The reason for the increased incidence of gallstones after gastrectomy is unclear. The predominant hypothesis is that the anatomical changes resulting from the surgery, especially in the event the vagus nerve is severed, affect contractility of the gallbladder, causing stasis and supersaturation of the bile that promote gallstone formation. In fact, the incidence of gallstones in patients who underwent pylorus-preserving gastrectomy is significantly low, supporting such hypothesis.[4].7)

Most cholelithiasis is asymptomatic gallstone without symptoms of biliary tract, acute cholecystitis, cholangitis, and pancreatitis. However, if gallstones that migrate to the gallbladder neck, gallbladder duct, or the common bile duct, symptoms such as the biliary colic, nausea, vomiting, fever, jaundice, etc. occur, and can be accompanied by complications such as inflammation, closure, etc. Asymptomatic cholelithiasis is usually treated by an observational treatment which performs monitoring at regular intervals until symptoms or complications occur. However, if the disease develops as a symptomatic gallstone, invasive treatment such as cholecystectomy should be performed. [9] Although the incidence of cholelithiasis with symptoms is marginal and pertains to about 10-20% of patients with gallstones. It was found that if additional cholecystectomy is performed on patients who underwent gastrectomy, the risk of increase in the rate of conversion to laparotomy and postoperative complications increased significantly compared to healthy people due to the increase in the operation time, adhesion of the surgery area, etc. [10].11) In other words, in the case of patients who underwent gastrectomy, the risk of gallstone formation increases at the same time as the risk increases during the treatment process as the disease progresses. Thus, efforts to reduce the risk of gallstone formation at the source is significant in that it will reduce the risk of surgical complications and the associated risks.

One of these efforts is to perform preventive cholecystectomy during a gastrointestinal surgery, and some studies have shown that preventive cholecystectomy can reduce the minimum additional risks.[12) - 14)] On the other hand, some studies also show that the likelihood of the outbreak of symptomatic cholelithiasis is low and that preventive cholecystectomy has no additional benefit in terms of postoperative mortality, morbidity and cost. So, there is some controversy about preventive cholecystectomy.[15)]

Among these, the administration of safer and more cost effective ursodeoxycholic acid (UDCA) is emerging as an alternative to the prevention of cholelithiasis. UDCA is a hydrophilic bile acid, a tertiary bile acid formed by liver or intestinal bacteria, present in less than about 3% of the normal bile acid reservoir. Since the early 1970s, UDCA has been used as an oral bile acid dissolution

therapy in cholelithiasis for which it is difficult to perform surgeries such as a cholecystectomy. Recently there are a number of studies showing that in addition to gallstones dissolution, UDCA administration inhibits gallstone formation compared to the placebo in patients with obesity who have shown a rapid weight loss due to the bariatric surgery or a low calorie diet.[16)-22)]

Similarly to the mechanism of gallstone dissolution, the preventive effect of UDCA for gallstones is known to be manifested by the inhibition of cholesterol supersaturation, reduction of nucleation factors, and improvement of the gallbladder motility.[23)] The effect of oral administration of UDCA is that cholesterol saturation in the gallbladder is reduced due to the increase of bile reservoir and changes in bile acid composition. And, cholesterol saturation is suppressed by reducing cholesterol secretion in the bile by decreasing the intestinal cholesterol absorption. It has also been reported that nucleating factors such as glycoprotein in bile are reduced and the gallbladder contractility is affected, thereby improving the gallbladder motility.

Because the preventive effect of UDCA for gallstones is related to its inherent function as a tertiary bile acid, it is expected that the preventive effect of UDCA will also be manifested in gallstones in patients with stomach cancer who have undergone gastrectomy in addition to the obesity patients who experienced a rapid weight loss. However, to date, there has been no study on the effect of UDCA on the preventive effect of gallstone formation after gastrectomy for patients with gastric cancer. Therefore, Daewoong Pharmaceutical Co., Ltd. developed DWJ1319 with UDCA 300 mg as the active substance and planned a phase 3 clinical study to evaluate efficacy and safety of DWJ1319 for the prevention of gallstone formation in patients with gastric cancer who underwent gastrectomy.

## 6. Overview of Investigational Product

### 6.1. Study Drug

1) Product name or code name: DWJ1319 (Ursa-D Capsule 300 mg)
2) Dosage form and appearance: Hard capsule of pink upper half and white lower half containing white to light yellow granules
3) Ingredient: Ursodeoxycholic acid 300 mg
4) Storage conditions: Tight container, store at room temperature (1-30℃)

### 6.2. Comparator

1) Product name or code name: Matching placebo of study drug
2) Dosage form and appearance: Hard capsule of pink upper half and white lower half containing white to light yellow granules
3) Ingredient: Matching placebo of study drug
4) Storage conditions: Tight container, store at room temperature (1-30℃)

### 6.3. Justification for Comparator

In this study, placebo will be used as a comparator. The purpose of placebo-control is to identify the pure pharmacological effects of the drug and to perform a reliable assessment by distinguishing from the natural course of the disease or adverse events due to other causes. The use of placebo also allows for randomization and blinding, minimizing bias in administering subjects and data analysis. Although the ethical issues of long-term placebo use may be addressed, the purpose of this study is to determine the preventive effect rather than the treatment of the underlying disease, so the risk of using placebo and the possible damages by participating in the study is not egregious.

### 6.4. Justification for Setting Dose of Study Drug

This study will be performed in three groups of placebo, 300 mg or 600 mg DWJ1319 to verify the

preventive effect of DWJ1319 for gallstone in patients with gastric cancer who underwent gastrectomy.

The preventive effect of UDCA for gallstone was confirmed in clinical studies in patients who experienced rapid weight loss, and an optimal dose was assessed as 600 mg/day. At this time, no significant difference was observed between the two treatment groups of 600 and 1200 mg.[19)]

Assessment of the gallbladder dissolution effect of UDCA in gallbladder patients by dose also showed that the gallbladder dissolution effect of UDCA was the highest at 500 mg. The gallbladder dissolution rate between the two treatment groups, 500 and 1000 mg/day, was not significantly different.[24)]

Because UDCA's gallstone prevention and treatment mechanism are related to its function as a tertiary bile acid and it is anticipated that the gallstone prevention mechanism will work the same even if the patient group is different, the optimal dose of UDCA for patients with gastric cancer is also expected to be 600 mg/day. However, since no study has confirmed the preventive effect of UDCA for gallstones in patients with gastric cancer who underwent gastrectomy, the objective is to verify the gallstone prevention effect in two treatment groups of DWJ1319 300 mg and 600 mg and to verify the optimal dose.

### 6.5. Production, Packaging, and Labeling of Investigational Product

Study drug and comparator will be produced and packaged at KGMP-compliant facilities by Daewoong Pharmaceutical Co., Ltd. and supplied to study sites. The labeling of the investigational product will be described pursuant to Article 69 (6) of the Regulations on Safety of Medicinal Products, etc., and the following contents will be included in this study.

1) Labeling for "for investigational use”
2) The code name of the product or the generic name of the active substance
3) Serial number and use-by (expiration) date or the re-testing date
4) Storage conditions
5) Name and address of the person approved for the clinical study protocol
6) Labeling that "it must not be used for purposes other than the clinical study"
7) Unique code: Investigational product number or randomization number

### 6.6. Supply, Distribution, and Storage of Investigational Product

The packaged investigational products are supplied by the sponsor Daewoong Pharmaceutical Co., Ltd. to each study site, and the managing pharmacist of the study site confirms the quantity and condition of the investigational product after its receipt. The managing pharmacist records details including the quantity of investigational product received, the quantity distributed to subjects, and the date of distribution. If there is a reason for return` during the treatment period of the investigational product, the returned quantity and the date of return should be recorded to determine the inventory quantity.

The examiner should check the quantity and storage status of the investigational product during the study period and make sure that the study is properly carried out by confirming that the investigational product is administered and controlled according to the protocol.

Investigational products should be stored and managed in an appropriate and safe space (e.g., space and storage with a locking device) in accordance with the storage conditions under the responsibility of the investigator or the managing pharmacist.

## 7. Target Diseases

Patients who were diagnosed with gastric cancer and underwent gastrectomy as treatment.

## 8. Inclusion and Exclusion Criteria for Subjects, Targeted Number of Subjects and Justification

### 8.1. Inclusion Criteria

1) Patients who voluntarily agree to participate in the study and sign the informed consent form
2) Patients at least 19 years of age at the time of informed consent
3) Patients who were diagnosed with gastric cancer and underwent any one of the following gastrectomies
   - Total gastrectomy
   - Distal gastrectomy
   - Proximal gastrectomy
4) Patients who underwent D1+ or D2 lymph node dissection
5) Patients with ECOG performance status scale ≤ 1 point (Appendix 1)
6) Life expectancy of at least 3 months
7) Patients who can be enrolled in the study within 2 weeks from gastrectomy

### 8.2. Exclusion Criteria

1) Patients with cholangitis, cholecystitis, non-functional gall bladder, or biliary obstruction
2) History of previous cholecystectomy
3) Patients who had gallstones detected in radiology conducted during screening (abdominal ultrasound, abdominal CT scan) or who had gallstones during gastrectomy
4) Patients who underwent pylorus-preserving gastrectomy
5) Patients who received or are currently receiving treatment for peptic ulcer (acute gastric·duodenal ulcer), pancreatitis, or colitis or enteritis (Crohn's disease, etc.) within 4 weeks prior to screening
6) Patients with varicose vein bleeding, fulminant hepatic failure, active hepatitis, liver cirrhosis, hepatic coma, or ascites, or those requiring liver transplantation
7) Patients with hypersensitivity to bile acid or ursodeoxycholic acid
8) Patients who require total parenteral nutrition for ≥ 1 week
9) Patients with BMI > 37 $kg/m^2$ at screening
10) Patients with uncontrolled diabetes (glycosylated hemoglobin (HbA1c) level ≥ 9%)
11) Patients with clinically significantly abnormal values in the screening test
    - ALT, AST, BUN, total bilirubin levels exceed the upper limit of normal by 2.5 times
    - eGFR <60 $mL/min/1.73\ m^2$
12) Patients who require prohibited concomitant medication(s) during the study period or cannot comply with the wash-out period for prohibited concomitant medication(s)
13) Pregnant or breast feeding women and women of childbearing age who are not using reliable contraceptive method during the study period or do not agree to maintain contraception during the study period
    - Methods of contraception: Use of at least two contraception methods among abstinence, subject's or his/her partner's surgical sterilization (vasectomy, etc.) or barrier methods using intrauterine device, condom, or spermicide is recommended.
14) Patients with history of drug or alcohol abuse within 5 years prior to study entry
15) Patients who were diagnosed with a cancer other than gastric cancer, basal cell or squamous epithelial skin cancer within 5 years prior to study entry
16) Patients with physical or mental dysfunction that participating in this study may expose them to the risks or confuse the results, or that cannot comply with the study requirements based on the judgment of the investigator.

17) Patients who received other investigational products within 30 days or ≥ 5 half-lives prior to screening, whichever is longer
18) Difficulty in performing the study, as judged by the investigator

### 8.3. Targeted Number of Subjects and Justification

1) Number of Subjects to be Recruited

Taking into account the 20% withdrawal rate, this clinical study plans to enroll a total of 519 subjects (173 per group).

2) Calculation Basis

The primary objective of this study is to assess the efficacy of the study drug compared with placebo in preventing gallstone formation after gastrectomy in patients with gastric cancer. If the efficacy of DWJ1319 300 mg or 600 mg versus placebo is statistically significant, the study drug is considered to demonstrate its superiority. The endpoints are the proportion of subjects with gallstone formation within 12 months after gastrectomy. The hypothesis to test this is as follows:

$H_0$ (null hypothesis): $P_{T1} = P_C$ and $P_{T2} = P_C$
$H_1$ (alternate hypothesis): $P_{T1} \neq P_C$ or $P_{T2} \neq P_C$

$P_{T1}$: Proportion of subjects with gallstone formation after receiving 600 mg of DWJ1319
$P_{T2}$: Proportion of subjects with gallstone formation after receiving 300 mg of DWJ1319
$P_C$: Proportion of subjects with gallstone formation after receiving placebo

For testing of each treatment group versus the placebo, the significance level of the test is not corrected because a sequential multiple test (twice) is performed using the fixed sequential method. The test sequence is 600 mg of DWJ1319 versus placebo and 300 mg of DWJ1319 versus placebo.

The following results were referenced to calculate the number of subjects to be tested.

| | Placebo | Ursodiol 300 mg | Ursodiol 600 mg | Ursodiol 1,200 mg |
|---|---|---|---|---|
| Study 1[19] (6M) | 32.14% (18/56) | 13.21% (7/53) | 1.64% (1/61) | 6.35% (4/63) |
| Study 2[4] (12M) | 16.94% (112/661) | - | - | - |
| Study 3[7] (12M) | 13.64% (6/44) | - | - | - |

In this clinical study, the incidence of gallstones in placebo was estimated to be 18%, which is the weighted average of Studies 1, 2 and 3, where Study 1 is the result of placebo in obese patients who underwent gastrectomy and Studies 2 and 3 are the adjusted results of placebo in gastric cancer patients who underwent gastrectomy. Since it is difficult to estimate the incidence of gallstone of DWJ1319 by each dose, 7%, which is the weighted average of the three Ursodiol treatment groups in Study 1 was estimated as the rate of gallstone formation for the study drug.

In addition to the above assumptions, the significance level is 5% for two-sided test, 80% for test power, and the minimum number of subjects for 1:1:1 assignment is as follows:

$$N = \frac{\left(Z_{1-2/\alpha} + Z_{1-\beta}\right)^2 \{P_T(1-P_T) + P_C(1-P_C)\}}{\delta^2}$$

$$= \frac{(1.96 + 0.842)^2 \{0.07(1-0.07) + 0.18(1-0.18)\}}{(0.07-0.18)^2} \approx 138$$

The minimum number of subjects required to have a power level of 80% at the 5% significant level is calculated as 138 per group. Taking into account the 20% withdrawal rate, this clinical study plans to enroll 173 people per group (total of 519).

## 9. Study Period

The overall study period is expected to be about 20 months, however, there may be a change in the duration if a situation arises that may affect the progress of the study such as difficulties in selecting the subjects.

Study period for each subject: It is about 54 weeks as follows:
• Screening period: 2 weeks
• Treatment period: 52 weeks (12 months)

## 10. Study Methodology

### 10.1. Study Design

This is a multicenter, randomized, double-blinded, placebo-controlled, phase 3 study. Subjects are patients who have been diagnosed with gastric cancer and underwent gastrectomy for treatment. Screening will be conducted on subjects who gave an informed consent to participate in the study. Subjects who meet the inclusion criteria and do not qualify as exclusion criteria will be randomly assigned to DWJ1319 300 mg (DWJ1319 300 mg, once a day), DWJ1319 600 mg (DWJ1319 300 mg, twice a day), or placebo (1: 1: 1). For randomization, stratified randomization using the study site, the lymph node resection range (D1+, D2), and the type of gastrectomy as the stratification factors will be performed and randomization will be performed within 2 weeks from gastrectomy. During the study period, the subjects will visit the study site at screening, randomization (Day 1) and at 3-month interval after the administration of investigational product (at 3, 6, 9, and 12 months) to undergo protocol-specified tests and procedures at each visit. However, any subject with formation of gallstone confirmed during the treatment period will terminate the study at the time of confirmation.

| Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|---|---|---|---|---|---|
| Until Week -2 | Day 1 | Month 3 ± 1 Week | Month 6 ± 1 Week | Month 9 ± 1 Week | Month 12 ± 1 Week |
| Screening | Randomization | Treatment period | | | |

### 10.2. Dosage and Administration, Method and Period of Administration

All randomly assigned subjects are orally administered with the investigational product twice a day, one capsule at a time, for a total of 52 weeks. The subjects take the investigational product in the morning and evening according to the investigator's instructions and if possible, take it at the same time each day.

[Method of administration by treatment group]

| Treatment group** | Method of administration | Study drug |
|---|---|---|
| Placebo | One capsule each of placebo for DWJ1319 in the morning and evening | Morning: ○, Evening: ○ |
| DWJ1319 300 mg | One capsule each of placebo for DWJ1319 in the morning and DWJ1319 in the evening | Morning: ○, Evening: ● |
| DWJ1319 600 mg | One capsule each of DWJ1319 in the morning and evening | Morning: ●, Evening: ● |

○: Placebo of DWJ1319, ●: DWJ1319

### 10.3. Drugs Allowed and Prohibited for Concomitant Use

Drugs other than the prohibited concomitant medication(s) may be taken during the study period. Medication(s) used for transient therapy in the event of other diseases or adverse events should be administered concomitantly based on consultation with the investigator. Information about all concomitant medication(s) taken at any time during the screening or this study (product name or ingredient name, purpose of administration, dosage, duration of administration, etc.) should be recorded in the case record form (CRF). However, information about the drugs administered during hospitalization due to gastrectomy before enrolling in the study (anesthetic, painkiller, physiological saline administered for the purpose of simple nutrition, glucose solution, plasma expander, electrolyte solvent, amino acid sap solution, comprehensive nutritional sap solution, mixed lipid sap, anti-thrombotic agents, post-surgery anti-inflammatory drugs (antibiotics, steroids), antiepileptics, antitussive expectorants, medications for controlling GI symptoms (diarrhea, constipation prevention, digestive medicine, etc.) need not be collected. However, among drugs used during the period of hospitalization due to gastrectomy, drugs to be used continuously after discharge depending on the patient's recovery status are included in those to be collected for concomitant medications.

The following drugs are prohibited for concomitant use during the study period:

| Medication class | Temporary (As needed) | Chronic | Restrictions |
|---|---|---|---|
| Tolbutamide | Not allowed | Not allowed | Concomitant use is prohibited from 48 hours prior to Visit 1 throughout the study |
| Cholestyramine colestipol | Not allowed | Not allowed | Concomitant use is prohibited from 48 hours prior to Visit 1 throughout the study |
| Medicinal charcoal, smectite<br>Antacids containing magnesium or aluminum hydroxide | Allowed | Not allowed | Concomitant use is prohibited during the study period after Visit 2. Temporary use is permitted, but a dosage interval of 4 hours should be maintained with the investigational product. |
| Estrogen<br>Oral contraceptive<br>Fenofibrate, bezefibrate | Not allowed | Not allowed | Concomitant use is prohibited from 4 weeks prior to Visit 1 throughout the study |
| Octreotide | Not allowed | Not allowed | Concomitant use is prohibited from 24 hours prior to Visit 1 throughout the study |
| NSAIDs (except for the low dose aspirin) | Allowed | Not allowed | Concomitant use is prohibited from 4 weeks prior to Visit 1 throughout the study; Only the temporary use is permitted |
| Ceftriaxone | Allowed | Not allowed | Concomitant use for 1 consecutive week or more is prohibited after Visit 2 throughout the study |
| Immunosuppressant (cyclosporine, tacrolimus) | Not allowed | Not allowed | Concomitant use from 1 week before Visit 1 throughout the study is prohibited |
| Parenteral nutrition | Allowed | Not allowed | Concomitant use for 1 consecutive week or more is prohibited after Visit 2 throughout the study |
| Bile salt extract or choleretics | Not allowed | Not allowed | Concomitant use is prohibited from 4 weeks prior to Visit 1 throughout the study; Temporary use of UDCA ≤ 25 mg/day is allowed, but the overall treatment period cannot exceed 1 month. |

### 10.4. Restrictions on Drugs, Diets and Activities before Visit

The following will be prohibited for the time specified before visiting the study site.

- For abdominal ultrasound, subjects should fast for at least 8 hours before each visit except for Visit 2 (all water, beverage, smoking, candy, etc. are restricted) and remain in a fasted state until the test is completed.
- Before each visit, the subjects should visit the hospital without taking the investigational product and take the investigational product after all test procedures are completed.

### 10.5. Randomization

#### 10.5.1. Assignment of the Treatment Group

Randomization is performed to ensure the scientific validity of the clinical study, to reduce bias that may occur during the clinical study, and to prevent the investigator's subjectivity in assigning subjects to each treatment group.

Based on the stratification factors, use the stratified block randomization method to randomly assign subjects to DWJ1319 300 mg, DWJ1319 600 mg, and placebo at 1:1:1 ratio. This will be done by each study site conducting the clinical study using the SAS proc plan procedure.

The stratification factor is set to two levels as follows:

- Lymph node resection range: D1+, D2
- Type of gastrectomy: Total gastrectomy, partial gastrectomy

The procedure for assigning subjects to each treatment group and prescribing and distributing the investigational product is as follows:

When the subjects are enrolled on Day 1, the investigator assigns to each subject a random assignment number based on the pre-generated randomization results, via the interactive web response system (IWRS). The investigator prescribes the investigational product using the random assignment number and the pharmacist distributes the investigational product with the same assigned number to the subject.

The random assignment number of the subject withdrawn from the study will also be withdrawn but retained. New subjects must be assigned new screening numbers and random assignment numbers.

#### 10.5.2. Blinding and Release of Blinding

This clinical study maintains a blind on the type of drug assigned to each subject on the investigator and subject. By maintaining the double-blinding on both the investigator and subject, it allows the investigator or subject to avoid bias in assessing treatment effects and adverse reactions. The study drug and the comparator in this clinical study should be manufactured in the same form so that it cannot be visually distinguishable for the double-blinding. The sub-portion packaging should also be the same.

If it is deemed necessary to remove the blinding due to the occurrence of an emergency situation that threatens the safety of the subject, the investigator should immediately notify Daewoong Pharmaceutical Co., Ltd. or the monitoring staff of the contract research organization delegated by Daewoong Pharmaceutical Co., Ltd. The monitoring staff is obliged to immediately contact the representative of Daewoong Pharmaceutical Co., Ltd. After obtaining the relevant information, the representative of Daewoong Pharmaceutical Co., Ltd. will discuss with the investigator to decide whether to remove the blinding and document the decision. After consulting with the sponsor, the investigator will access the unblinding screen of the randomization website, input necessary

information, obtain information on the investigational product of the subject, print the screen, sign it, and keep it under the investigator's file.

In the event that it is impossible to immediately get in contact with Daewoong Pharmaceutical Co., Ltd., the sponsor, the investigator will access the unblinding screen of the randomization website, input necessary information, obtain information on the investigational product of the subject, print the screen, sign it, and keep it under the investigator's file. In such case, the investigator must notify Daewoong Pharmaceutical Co., Ltd. as soon as possible of the unblinding of the double-blindness, and document the reasons for unblinding without consulting the sponsor.

If the investigator finds out the subject's code during the study, the investigator should endeavor to eliminate bias in assessing efficacy and safety.

After completing the study, the investigator will resolve any issues on all data through Data Clarification Form (DCF). Once the database is confirmed to be complete and accurate, the data will be locked and random assignment code information will be released. Subsequent changes to the database are possible only with the informed consent of the sponsor and the database administrator.

# 11. Observations, Clinical Tests, and Observational Examination Method

## 11.1. Clinical Study Schedule

The clinical study is conducted according to the following schedule:

| | Screening | Baseline | Treatment | | | |
|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 / Early Termination[1)] |
| Duration | From Week -2 Day -1 | Day 1 | Month 3 (±1 week) | Month 6 (±1 week) | Month 9 (±1 week) | Month 12 (±1 week) |
| Informed consent[2)] | ○ | | | | | |
| Demographic survey | ○ | | ○[3)] | ○[3)] | ○[3)] | ○[3)] |
| Medical/surgical history | ○ | ○ | | | | |
| Physical examination | ○ | | | ○ | | ○ |
| Vital signs | ○ | ○ | ○ | ○ | ○ | ○ |
| Inclusion/exclusion criteria | ○ | ○ | | | | |
| Randomization | | ○ | | | | |
| Abdominal ultrasound[4)] | ○[5)] | | ○ | ○ | ○ | ○ |
| Abdominal CT scan | ○[5)] | | | ○ | | ○ |
| Assessment of bile reflux symptoms | | ○ | ○ | ○ | ○ | ○ |
| Upper gastrointestinal endoscopy | | | ○ | | | ○ |
| Laboratory tests | ○[6)] | | ○[7)] | ○ | ○[7)] | ○ |
| Pregnancy test[8)] | ○ | | | | | |
| Prescription of investigational products | | ○ | ○ | ○ | ○ | |
| Treatment compliance | | | ○ | ○ | ○ | ○ |
| Adverse events | | | ○ | ○ | ○ | ○ |
| Prior/concomitant medications[9)] | ○ | ○ | ○ | ○ | ○ | ○ |

1) For a dropout or early termination, the procedures for Visit 6 will be performed.
2) The informed consent form will be obtained in writing prior to study initiation after explaining the objectives and details of the study to the subjects. The informed consent should be obtained prior to any study procedures.
3) At the screening visit, the demographic information (subject initials, gender, date of birth, smoking status and alcohol use, weight, height, BMI, etc.) will be collected. Only the body weight is measured at each subsequent visit.
4) Will be measured in a fasted state (including the investigational product) on the day of visit. It not in a fasted stated on the day of visit, the test will be conducted by re-visiting during the imaging test window (regular visit ± 2 weeks). A subject with gallstone formation confirmed during the study period will terminate the study at the time of confirmation.
5) If there is a recent radiology result (within 6 weeks before screening), the result can be used as a screening test.
6) Abdominal CT scan and upper gastrointestinal endoscopy (once in 3 months or 12 months) is a periodic examination that is usually performed in connection with gastrectomy. If there is a result for the corresponding examination, result of the periodic examination shall be collected and utilized.
7) If the test result performed during the screening test does not meet the inclusion/exclusion criteria, re-testing may be conducted only once.
8) At Visits 3 and 5, Liver function tests (ALT, AST, ALP, γ-GTP, and total bilirubin) among laboratory tests will be performed.
9) Urine HCG test will be performed only in women of childbearing age and the result should be confirmed prior to the administration of the investigational product.

10) Any drug that has been administered from 4 weeks before the screening visit throughout the study or is currently administered should be recorded.

## 11.2. Observation Items and Methods

### 11.2.1. Acquisition of Informed Consent

The investigator should explain in detail the purpose and contents of the study to the subjects who intend to participate in this study. The subject confirms the information about the study, and signs the informed consent form by hand. The informed consent must be obtained prior to performing all procedures associated with the study. After receiving the informed consent of the subject, the investigator will give the screening number in the order of participation in the study.

### 11.2.2. Demographic Survey

During the screening visit, a demographic survey on the status of the informed consent, date of consent, subject's initial, gender, date of birth, weight, height, BMI, smoking and drinking status, etc. is conducted. At Visits 3, 4, 5, 6 and at the time of early termination/dropout, only the body weight is measured.

### 11.2.3. Medical History/Prior Surgery

A detailed examination and recording of medical history and prior surgery of the subjects are carried out through a medical examination by interview and by reviewing past medical records. For the medical history including surgical operations, allergies, etc., name of the diagnosis/surgery, status of continuation, etc. are recorded. For other baseline characteristics, information on histological findings of gastric cancer (including TNM stage), types of gastrectomy, types of reconstruction, lymph node dissection, etc. is collected.

### 11.2.4. Physical Examination and Vital Signs

Physical examinations will be conducted at Visits 1, 4 and 6 or at the time of early termination/dropout. The investigator will perform the physical examination through interviewing, examining, facilitating, and stethoscoping, etc. of subjects, and the result is recorded on the case record form. Test items include general appearance, skin/mucosa, lymphatic system, cephalus/cervical part, eye/ear/nose/ throat, gastrointestinal, cardiovascular, respiratory, neurological and musculoskeletal systems. And, symptoms due to the underlying disease of this study will not be collected.

Vital signs (blood pressure, pulse) are measured at each visit. Pulse and blood pressure should be measured after the subject has been sitting for 5 minutes, and always on the same arm for evaluation.

### 11.2.5. Abdominal Ultrasound

Abdominal ultrasound is performed at Visits 1 (baseline), 3, 4, 5 and 6, or at the time of early termination/withdrawal to determine gallstone formation. At Visits 3 and 6, the abdominal ultrasound should be performed prior to the upper gastrointestinal endoscopy. Also, if abdominal ultrasound is performed on the same day as abdominal CT scan, the abdominal ultrasound should be performed prior to abdominal CT scan. Patients should remain in a fasting state for at least 8 hours before the test up until the end of the test. If the patient is unable to do so, the visit process should stop to reschedule it. If it is difficult to perform abdominal ultrasound on the regular visit due to the testing schedule of each study site, it may be done within regular visit ± 2 weeks.

The investigator confirms through abdominal ultrasound whether gallstones have formed in areas including the liver, gallbladder, and bile ducts. If gallstone formation is confirmed, an ultrasound

photograph that confirms the formation of gallstones should be stored as an evidence document. Even if gallstone formation is not confirmed, ultrasound photographs that are available for the following four sites should be kept as an evidence document.

1) A subcostal scan that allows monitoring both portal veins
2) An intercostal scan that allows monitoring the right portal vein
3) A subcostal scan that allows monitoring the full length of the gallbladder
4) An intercostal scan that allows monitoring the full length of the gallbladder

### 11.2.6. Abdominal CT Scan

An abdominal CT scan is performed at Visit 1 (baseline), Visit 4 and Visit 6. Patients should remain in the fasting state for at least 8 hours before the test. If the patient is unable to do so, the visit process should stop to reschedule it. If it is difficult to perform the abdominal CT scan on the day of a regular visit due to the test schedule of each study site, it can be performed within regular visit ±2 weeks.

The investigator obtains pre-contrast and post-contrast abdominal CT images and confirms gallstone formation in the liver, gallbladder, and bile ducts.

In this case, if the investigator judges that the CT scan of parts including the liver, gallbladder, and bile duct, is enough to identify gallstones, the CT scan of parts other than the abdominal CT (e.g., stomach CT, whole body CT, etc.) can also be used in place of the abdominal CT.

### 11.2.7. Determination of Gallstones

The diagnosis of gallstone formation is based primarily on the results of the abdominal ultrasound and is supplemented by abdominal CT scan results. If the results of the two tests differ, abdominal ultrasound result should be considered first for gallbladder gallstones, and both abdominal ultrasound and abdominal CT should be considered in the case of bile duct gallstones or intrahepatic bile duct gallstones.

If the abdominal ultrasound results satisfy the following criteria, it will be considered as a gallstone in the gallbladder.[9),25)-28)] If any one of the criteria is not met, or there is only hyperechoic shadow without posterior acoustic shadow, it is judged as negative for gallstone formation.

1) Hyperechoic shadow (echo sign)
2) Posterior acoustic shadow
3) The movement of echo according to changes in body position (movement, gravitational dependence)

The bile duct gallstone is distinguished by abdominal ultrasound that shows a hyperechoic substance with posterior acoustic shadow or an enlargement of peripheral bile duct around the echo, and is determined by compiling the results of abdominal CT scans.
Gallstones should be distinguished from biliary sludge and should be determined to be biliary sludge if the following criteria are met:

1) Hypoechoic shadow without accompanying acoustic shadow
2) Moves according to changes in body position and has a characteristic to form a horizontal plane

The investigator will document in the case record form (CRF) the presence of gallstones, the presence of biliary sludge, and the location of gallstones (gallbladder, common bile duct, intrahepatic bile duct), size and number of gallstones.

### 11.2.8. External Investigator's Assessment of the Imaging Test Results for Gallstone Formation

To ensure the reliability of the imaging test results (abdominal ultrasound and abdominal CT scan), independent external investigators evaluate the results of imaging tests to determine whether gallstones have formed. External investigators consist of three independent investigators who have not participated in the corresponding clinical study.

The external committee member will independently check the results of the imaging test without any exchange of opinions and state whether gallstones have formed or not. The assessment is based on abdominal ultrasound and CT imaging data collected from all study sites and is randomly arranged regardless of the number or the order of the visit of the subjects so that researchers can conduct an assessment without being affected by the time of shooting. The assessment results on which at least two of the three external investigators agree on will be selected.

### 11.2.9. Assessment of Biliary Reflux Symptoms and Upper Gastrointestinal Endoscopy

The assessment of symptoms for a biliary reflux will be conducted at Visits 2 (baseline), 3, 4, 5 and 6, or at the time of early termination/withdrawal to determine the gallstone formation. The subjects completes a questionnaire (Appendix 2) in three areas including the frequency, strength, and the level of pain of the representative symptoms of biliary reflux (upper abdominal pain, heartburn, and nausea).

In addition, the investigator will perform an upper gastrointestinal endoscopy at Visits 3 and 6 to confirm the actual reflux of bile and record the results. There is no need for a separate endoscopy, but endoscopy results under routine clinical practices can be collected and used.

To diagnose bile reflux during the upper gastrointestinal endoscopy, the investigator will evaluate the status of bile reflux (Y/N) by observing the remnant stomach or the anastomotic area and determine it as bile if a yellow liquid is observed in the assessed area. If bile reflux is observed, gastritis is assessed as well according to the following criteria: [29).30)]

1) Grade 0: No flare on mucous membrane or the remnant stomach or anastomotic area.
2) Grade 1: Mild redness is observed in the mucous membrane of the remnant stomach or anastomotic area.
3) Grade 2: A comb-shaped redness is observed on mucous membrane of the remnant stomach or anastomotic area.
4) Grade 3: Severe redness and edema are observed on mucous membrane of the remnant stomach or throughout the anastomotic area.

### 11.2.10. Laboratory Tests

Laboratory tests are carried out using the Central lab and are performed in a fasted state at Visits 1, 4 and 6 or at the time of early termination/withdrawal. If screening results do not meet the inclusion/exclusion criteria, they may be retested only once. Women of childbearing age should be checked for pregnancy through a urine hCG test at Visit 1. In addition, if it is deemed necessary based on the investigator's judgment, additional tests may be conducted.

Laboratory test items are as follows:

| | |
|---|---|
| **Hematology** | WBC, RBC, Hemoglobin (Hb), Hematocrit (Hct), Platelet count, WBC differential count (Neutrophil, Lymphocyte, Monocyte, Eosinophils, Basophils) |

| | |
|---|---|
| **Biochemical test** | Glucose, Total protein, Albumin, Total cholesterol, Triglyceride, Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), gamma-glutamyl transferase (γ-GTP), Uric acid, Creatinine, sodium, potassium, chloride, calcium, HbA1c*, eGFR |
| **Urinalysis** | Bilirubin, urobilinogen, Blood, Glucose, pH, Protein, Specific Gravity |
| **Pregnancy test**** | Urine HCG |

† HbA1c: It will be performed once at screening, and if there is a test result within the last 3 months, it can be replaced with the screening test result.

** Pregnancy test: It is performed only for women of childbearing age.

In addition, only the liver function tests (ALT, AST, ALP, γ-GTP and total bilirubin) among the biochemical tests are performed at Visits 3 and 5.

### 11.2.11. Adverse Events

The investigator will be trained to voluntarily report from time to time when an adverse event occurs to the subject. In addition, the investigator should check the occurrence of the adverse events through consultation and interviews at regular visits during the study period.

The investigator should review the results of the laboratory tests and evaluate whether the results diverging from the normal value are clinically significant. If it is considered that there is a clinical significance when before and after the administration of the investigational product are compared, it should be evaluated as an adverse event. Also, based on the physical examination results, significant changes in the physical examination findings which are consistent with the definition of an adverse event after the administration of the investigational product should be also assessed as an adverse event.

Investigation of adverse events includes the dates of onset and disappearance, severity, treatment, outcomes, causal relationship with the investigational product, actions taken in relation to the investigational product, suspected drugs other than the investigational product and seriousness, etc.

### 11.2.12. Prior/Concomitant Medications

The investigator should be aware of the drugs that are allowed and prohibited for concomitant use in this study, investigate drugs used concomitantly by subjects, and confirm whether the study protocol is followed.

To identify prior medications, the information (product name or ingredient name, purpose of administration, dose, duration of administration, etc.) of the drugs administered within 4 weeks based on the screening visit should be investigated. In addition, changes in concomitant drugs should be confirmed at every visit, and the changes should be recorded in the case record form.

### 11.2.13. Prescription of Investigational Products and Treatment Compliance

Subjects who meet the inclusion criteria and do not correspond to the exclusion criteria are randomly assigned to the study arm or the control group at Visit 2 to receive the investigational product. The investigator will prescribe the investigational products with a quantity of approximately 3 months + 1 week (99 days) taking into account the next visit schedule at Visits 2, 3, 4 and 5. And, at Visits 3, 4, 5, 6 or visits for the early termination/withdrawal, the unused portion of the investigational products that are prescribed in previous visits will be collected from subjects to verify the treatment compliance. Subjects whose treatment compliance does not exceed 85% will receive retraining for the administration of investigational products.

### 11.3. Visit Schedule

#### 11.3.1. Visit 1 (screening, Week - 2)

The subjects who are scheduled to participate in this clinical study will hear explanations about the study from the investigator and perform screening visits according to the following procedure: The investigator will use the information obtained from Visit 1 to determine if the subject is eligible to participate in the study.

- The informed consent will be obtained from subjects before the study procedures, and the screening number will be distributed.
- Demographics are collected.
- Information about the medical history/prior surgery is collected.
- Information on prior/concomitant medications is collected.
- A physical examination is carried out.
- Vital signs (blood pressure, pulse) are measured.
- Laboratory tests (hematology, biochemistry, urinalysis) are carried out.
- For women of childbearing age, a pregnancy test is carried out.
- Abdominal ultrasound is performed to confirm the presence of gallstones.
- Abdominal CT scan is performed to confirm the presence of gallstones.
- The inclusion/exclusion criteria are verified.
- The subsequent visit dates are determined.

#### 11.3.2. Visit 2 (randomization and administration of investigational products, Day 1)

Visit 2 will take place within two weeks after the screening (Visit 1). If the subject is suitable for participating in the clinical study, the following procedures will be performed:

- Vital signs (blood pressure, pulse) are measured.
- Changes in the medication history and therapeutic potential are checked compared to previous visits.
- Changes in the medical history/prior surgery are checked compared to previous visits.
- The inclusion/exclusion criteria are re-verified.
- Randomization is performed.
- Investigational products are prescribed, and guidance is provided for taking medications.
- A questionnaire to evaluate the symptoms of biliary reflux is prepared.
- The subsequent visit dates are determined.

#### 11.3.3. Visit 3 (treatment period, 3 months ± 1 week)

At visit 3, the following procedures will be performed at 3 months ± 1 week after Visit 2.

- Among the demographic survey, only the body weight is measured.
- Vital signs (blood pressure, pulse) are measured.
- Changes in the medication history and therapeutic potential are checked compared to previous visits.
- Adverse events are checked.
- Abdominal ultrasound is performed. It should be performed prior to upper gastrointestinal endoscopy.
- Upper gastrointestinal endoscopy is performed to check bile reflux.

- A questionnaire to evaluate the symptoms of biliary reflux is prepared.
- Among laboratory tests, liver function tests (ALT, AST, ALP, γ-GTP and total bilirubin) are performed.
- Unused medicinal products are collected, and treatment compliance is checked.
- Investigational products are prescribed, and guidance is provided for taking medications.
- The subsequent visit dates are determined.

**11.3.4. Visit 4 (treatment period, 6 months ± 1 week)**

At Visit 4, the following procedures will be performed at 3 months ± 1 week after Visit 2.

- Among the demographic survey, only the body weight is measured.
- A physical examination is carried out.
- Vital signs (blood pressure, pulse) are measured.
- Changes in the medication history and therapeutic potential are checked compared to previous visits.
- Adverse events are checked.
- Abdominal ultrasound is performed. It should be performed prior to abdominal CT scan.
- Abdominal CT scan is performed.
- A questionnaire to evaluate the symptoms of biliary reflux is prepared.
- Laboratory tests (hematology, biochemistry, urinalysis) are carried out.
- Unused medicinal products are collected, and treatment compliance is checked.
- Investigational products are prescribed, and guidance is provided for taking medications.
- The subsequent visit dates are determined.

**11.3.5. Visit 5 (treatment period, 9 months ± 1 week)**

At Visit 5, the following procedures will be performed at 9 months ± 1 week after Visit 2.

- Among the demographic survey, only the body weight is measured.
- Vital signs (blood pressure, pulse) are measured.
- Changes in the medication history and therapeutic potential are checked compared to previous visits.
- Adverse events are checked.
- Abdominal ultrasound is performed.
- A questionnaire to evaluate the symptoms of biliary reflux is prepared.
- Among laboratory tests, liver function tests (ALT, AST, ALP, γ-GTP and total bilirubin) are performed.
- Unused medicinal products are collected, and treatment compliance is checked.
- Investigational products are prescribed, and guidance is provided for taking medications.
- The subsequent visit dates are determined.

**11.3.6. Visit 6 (termination visit, 12 months ± 1 week)**

At Visit 6, the following procedures will be performed at 12 months ± 1 week after Visit 2.

- Among the demographic survey, only the body weight is measured.
- A physical examination is carried out.
- Vital signs (blood pressure, pulse) are measured.

- Changes in the medication history and therapeutic potential are checked compared to previous visits.
- Adverse events are checked.
- Abdominal ultrasound is performed. It should be performed prior to the upper gastrointestinal endoscopy and the abdominal CT scan.
- Abdominal CT scan is performed.
- Upper gastrointestinal endoscopy is performed to check the bile reflux.
- A questionnaire to evaluate the symptoms of biliary reflux is prepared.
- Laboratory tests (hematology, biochemistry, urinalysis) are carried out.
- Unused medicinal products are collected, and treatment compliance is checked.

#### 11.3.7. Early Termination Visit

Among randomly assigned subjects, for subjects who meet the early termination or the withdrawal criteria and the study has to terminate before Visit 6, the early termination visit will be conducted. As for the procedures for early termination/dropout, the same test and assessment in accordance with the procedures carried out at Visit 6 (termination visit) will be conducted. However, abdominal ultrasound/abdominal CT scan can be waived if there is an abdominal ultrasound within 3 months prior to an early termination visit or an abdominal CT scan within 6 months prior to the such visit.

- Among the demographic survey, only the body weight is measured.
- A physical examination is carried out.
- Vital signs (blood pressure, pulse) are measured.
- Changes in the medication history and therapeutic potential are checked compared to previous visits.
- Adverse events are checked.
- Abdominal ultrasound is performed. It should be performed prior to the upper gastrointestinal endoscopy and the abdominal CT scan. However, in case of an early termination due to gallstone formation, the test may be waived.
- Abdominal CT scan is performed. However, in case of an early termination due to gallstone formation, the test may be waived.
- A questionnaire to evaluate the symptoms of biliary reflux is prepared.
- Laboratory tests (hematology, biochemistry, urinalysis) are carried out.
- Unused medicinal products are collected, and treatment compliance is checked.

#### 11.3.8. Unscheduled Visit

If there is a need for medical treatment according to the examination results of adverse events and regular visits and the visit was made on a day that is not a regular visit due to changes in the use of the investigational product, follow-up, etc. of adverse events after the clinical study, corresponding information should be recorded in the relevant forms including the case record form. The schedule for regular visits should not change as a result of unscheduled visits.

## 12. Expected Side Effects and Precautions for Use

Please refer to Appendix 3 Expected Side Effects and Precautions for Use.

## 13. Discontinuation and Withdrawal Criteria

### 13.1. Criteria for Withdrawal from Study

A subject who has signed an informed consent may stop participating in the study at any time during the study period. The reasons for early withdrawal of subjects are as follows:

1) Subject's voluntary termination of the study (withdrawal of consent): The investigator confirms that the reason for the withdrawal of consent is not due to adverse events, etc.
2) In case of violation of inclusion/exclusion criteria
3) If the subject does not visit (failure to follow-up)
4) If it is difficult to carry out the study due to adverse events
   : the study may be discontinued at the discretion of the investigator or the subject, regardless of the causal relationship with the investigational product.
5) If it is difficult to continue the study at the discretion of the investigator due to the recurrence, etc. of gastric cancer during the study period
6) If the study cannot proceed further based on other judgment of the investigator

For subjects who have withdrawn early after randomization, the final evaluation will be conducted according to the schedule for early termination visit regardless of the reason. If they refuse a termination visit or cannot be reached by phone, a call should be made continuously so that all unused investigational products can be returned. The reason(s) for dropout from the clinical study should be recorded in the final assessment section of the case record form.

### 13.2. Early Termination of Study

Patients who have been confirmed for gallstone formation through the abdominal ultrasound during the post-randomization treatment period should stop participating in the study at the time of confirmation. The final assessment should be performed according to the schedule for visit 6/early termination. The subjects who are terminated early according to the early termination criteria are judged to have completed the study according to the study protocol instead of a dropout.

### 13.3. Criteria for Study Discontinuation

The principal investigator may discontinue part or all of the study in consultation with the sponsor if it is judged that it is not wise to continue the study in light of the results observed in the study. If the principal investigator prematurely terminates or suspends the clinical study without prior agreement with the sponsor, the principal investigator should immediately notify the sponsor and the IRB of the study site, and provide a detailed explanation of the early termination and discontinuation.

The IRB may decide to terminate early or discontinue the study if the ongoing study is conducted differently from the IRB's request or decisions, or if there is a significant unexpected risk to the subject. In this case, the IRB will immediately notify the head of the study site or the principal investigator of the decision and its reasons. In this case, the investigator will notify the sponsor immediately and submit a detailed explanation of the early termination and discontinuation.

The sponsor may discontinue part or all of the clinical study for safety or managerial reasons. If the study is terminated or discontinued early, the sponsor should promptly report such fact and reasons to the principal investigator and the Minister of Ministry of Food and Drug Safety. In the case of multicenter studies, principal investigators of other study sites conducting the study should also be notified of such fact and reasons in writing. In this case, the principal investigator will notify the IRB immediately and submit a detailed explanation of the early termination and discontinuation.

In the event of an early termination or discontinuation of the study, the principal investigator should immediately notify the subjects of such fact and ensure that appropriate measures and follow-up investigations are carried out. The principal investigator should organize the case record form,

progress status and results of the study until the time of termination and provide them to the sponsor, and return the investigational products and all test-related data and products to the sponsor.

### 13.4. Handling of Protocol Deviations

The principal- and sub-investigators should be fully familiar with and thoroughly implement the protocol to avoid protocol deviations. If a deviation occurs during the study period, the investigator will document the deviation and take appropriate actions to correct the deviation.

As a rule, in the event of a critical deviation of protocol, the subject should be dropped from the analysis (excluded from the PP analysis), and the corresponding cases are as follows:

① If the inclusion/exclusion criteria are not met

② If the compliance of the investigational product is less than 80%

③ If the patient has received medication or treatment that may have a significant impact on the outcome of the study

In addition, for minor deviations of protocol, which are judged to have no effect on the interpretation of the study results, the degree and reasons for deviation or delay should be accurately recorded and included in the PP analysis by comprehensively considering whether they had an impact on the study.

## 14. Statistical Analysis Method

### 14.1. Definition of Analysis Set

#### 14.1.1. Analysis Set for Efficacy Assessment

Both Full Analysis Set (FAS) and Per-Protocol (PP) analyses are carried out for efficacy data, and as a rule, the results of the FAS will be interpreted as the main analysis results.

1) Full Analysis Set (FAS)
Among patients who received at least one dose of the investigational product, those who have not violated the inclusion/exclusion criteria and were subjected to at least one assessment of gallstone formation after randomization.

2) Per-Protocol (PP) Set
The PP Set is composed of subjects who have completed the study without a significant deviation of the protocol that could affect the efficacy of the FAS. The subjects who were terminated according to the early termination criteria of Section 13.2 are included in the PP Set. For subjects who are excluded from the PP Set for other significant deviations, the reasons will be clarified and documented before releasing blinding.

#### 14.1.2. Analysis Set for Safety Assessment

It will consist of all subjects who have received the investigational product at least once among randomly assigned subjects.

### 14.2. General Principles of Result Analysis

All statistical analyses use SAS® 9.3 or higher and perform a two-sided test at a significance level of 5%.
The descriptive statistics (mean, standard deviation, minimum, median, and maximum) are provided for the continuous data (age, weight, height, BMI, etc.), and the frequency and proportion are provided for the categorical data (sex, etc.).

If a missing value occurs due to a subject withdrawing before the end of the clinical study or a missing test at a certain point in time, etc., the analysis will be carried out without replacing the data unless otherwise specified and will be processed as missing (Observed Case).

### 14.3. Demographic Surveys and Other Baseline Characteristics

The demographics of all subjects included in the FAS are assessed for each treatment group. For the continuous data, descriptive statistics (mean, standard deviation, minimum, median, and maximum) will be provided, and the treatment groups should be compared using the ANOVA or Kruskal- Wallis test. Frequency and proportion are provided for the categorical data, and the treatment groups are compared using the chi-square test or the Fisher's exact test.

### 14.4. Efficacy Analysis

#### 14.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of patients with gallstone formation within 12 months after gastrectomy according to the assessment by an external investigator.

For the superiority testing of DWJ1319 over placebo on the incidence of gallstone formation, the sequential multiple testing will be performed for each treatment group according to the fixed sequence method.

- Step 1: Superiority testing for DWJ1319 600 mg compared with placebo (5% significance level)
- Step 2: Superiority testing for DWJ1319 300 mg compared with placebo (5% significance level)

As DWJ1319 600 mg is expected to be relatively more effective in preventing gallstones compared to DWJ1319 300 mg, the efficacy assessment of DWJ1319 600 mg versus placebo is given priority.

The step 2 test can be performed only if the result of step 1 test is statistically significant, and the conclusions about the superiority of DWJ1319 over placebo will be drawn based on the test result from each step. If the result of step 1 test is not statistically significant, the step 2 test will not be performed, and it will be concluded that both treatment groups of DWJ1319 have failed to demonstrate the superiority over placebo.

The test in each step will use the logistic regression model with the lymph node resection range and the method of gastrectomy as covariates and present the frequency and proportion along with 95% confidence interval of subjects who have formed gallstone within 12 months by treatment group.

#### 14.4.2. Secondary Efficacy Endpoints

1) Proportion of patients with gallstone formation within 3, 6, 9, and 12 months after gastrectomy

The frequency and proportion of subjects with gallstone formation at each time point and the corresponding 95% confidence interval are provided for each treatment group. And the difference in the gallstone onset rate between each treatment group of DWJ1319 and the placebo is analyzed using a logistic regression model with the lymph node resection range and the type of gastrectomy as covariates.

2) Proportion of patients with gallstone formation within 3, 6, 9 months after gastrectomy according to the assessment by an external investigator

The frequency and proportion of subjects with gallstone formation at each time point and the corresponding 95% confidence interval are provided for each treatment group according to the

assessment of outside researchers. And the difference in the gallstone onset rate between each treatment group of DWJ1319 and the placebo is analyzed using a logistic regression model with the lymph node resection range and the type of gastrectomy as covariates.

3) Proportion of patients with biliary sludge within 3, 6, 9, 12 months after gastrectomy

The frequency and proportion of subjects with the formation of biliary sludge at each time point and the corresponding 95% confidence interval are provided for each treatment group. And the difference in the biliary sludge onset rate between each treatment group of DWJ1319 and the placebo is analyzed using a logistic regression model with the lymph node resection range and the type of gastrectomy as covariates.

4) Time taken for gallstone formation

The period from the date of gastrectomy to the date of gallstone formation is calculated based on the following criteria.

Early termination due to gallstone formation within 12 months after gastrectomy or completion due to gallstone formation at 12 months will be treated as an incidence, and the period until the early termination or completion will be computed.

If gallstones are not formed until the completion of the clinical study, it will be treated as cut-off data, and the time to completion will be calculated. If the patient is withdrawn within 12 months after the gastrectomy, it will be treated as cut-off data and the time to dropout will be calculated.

The time taken up to gallstone formation will be presented for each treatment group, and as for the time taken to gallstone formation, comparison between each treatment group of DWJ1319 and the placebo will be analyzed using the cox proportional hazards regression model with the lymph node resection range and gastrectomy as prognostic factors.

### 14.4.3. Other Efficacy Endpoints

1) Changes in the bile reflux symptoms from baseline value (score for each area and the overall score) at 3, 6, 9, and 12 months

For scores of questionnaire on bile reflux symptoms, the score of each typical symptom (upper abdominal pain, heartburn, nausea) and the total score of symptoms will be presented in three categories which are frequency, intensity, and the level of distress.

Descriptive statistics (mean, standard deviation, minimum, median, and maximum) for changes in the bile reflux symptom score and changes compared to the baseline value at each time point are provided for each treatment group. And the difference in the changes in the bile reflux symptom score between each treatment group of DWJ1319 and the placebo is analyzed using the analysis of covariance with the lymph node resection range and the type of gastrectomy as covariates.

2) Percentage of subjects who developed biliary reflux according to the upper gastrointestinal endoscopy at 3 and 12 months

The frequency and proportion of subjects with biliary reflux at each time point and the corresponding 95% confidence interval are provided for each treatment group. And the difference in the biliary reflux onset rate between each treatment group of DWJ1319 and the placebo is analyzed using a logistic regression model with the lymph node resection range and the type of gastrectomy as covariates.

3) Percentage of subjects with significant AST and ALT abnormalities at 6 and 12 months

The frequency and percentage of subjects for whom the AST and ALT of the laboratory test were

determined to be clinically significant abnormalities at the 6th and 12th month after gastrectomy were presented, and the difference between each dose of DWJ1319 versus placebo for the clinically significant abnormal percentage are analyzed using a logistic regression model with the lymph node resection range and type of gastrectomy as covariates.

### 14.5. Safety Analysis

Safety analysis is performed for the safety analysis set. Safety endpoints are adverse events, laboratory tests, vital signs, and physical examinations. The baseline for each safety endpoint should use the results of the last assessment performed prior to the first dose of the investigational product.

#### 14.5.1. Adverse Events

Summary and analysis of adverse events are performed on treatment-emergent adverse events (TEAE). Adverse events following treatment are those that did not occur before the treatment, but the adverse events that occurred after the treatment or adverse events that became worse even if they are symptoms that existed prior to the treatment.

Descriptive statistics (number of subjects, incidence, and number of cases) will be presented by treatment group for the treatment emergent adverse event (TEAE), adverse drug reaction (ADR), and serious adverse event (SAE), and the two-sided 95% confidence interval for the incidence will also be presented. The differences in proportions between the treatment groups will be compared using the chi-square test or Fisher's exact test. All adverse events (TEAE) that occurred after the drug administration, adverse drug reactions (ADR) and serious adverse events (SAE) should be coded according to System Organ Class (SOC) and Preferred Term (PT) using MedDRA. The number of subjects who have manifested coded adverse events, incidence, number of cases, etc. should be presented for each treatment group. The relevance with the investigational product and severity will be assessed and presented by categorizing by SOC. In addition, a detailed report should be written about SAEs.

#### 14.5.2. Laboratory Tests and Vital Signs

Descriptive statistics (mean, standard deviation, minimum, median, and maximum) will be presented by treatment group for the measurements at each time point and the change from baseline after the administration of the investigational product, and the frequency and proportion will be presented for categorical measurement results.

The treatment groups will be compared by ANOVA or a Kruskal–Wallis test for continuous data, and by the chi-square test or Fisher's exact test for categorical data.

For laboratory tests, classification should be made into a normal or not clinically significant abnormality and clinically significant abnormality. A shift table will be presented for changes in the post-administration compared to pre-administration of the investigational product. The chi-square test or the Fisher's exact test will be used to analyze the proportion of patients who have changed to clinically significant abnormalities post-dose at a not clinically significant abnormality.

#### 14.5.3. Physical Examination

For each item of physical examination, the frequency and proportion of normal/abnormal subjects will be provided.

## 15. Safety Assessment Criteria and Methods, and Reporting Methods

### 15.1. Method of Safety Assessment

Items for safety assessment include adverse events, vital signs, laboratory tests, and physical examinations. The investigator will examine the subjects at each visit and record all safety assessments performed according to the scheduled procedures.

The results of the laboratory tests are classified into normal and abnormal (NCS, CS) according to the normal range. If the laboratory test result after the administration of the investigational product is judged to be clinically significant compared to before administration, conditions for the abnormal value should be recorded, and it should be assessed as an adverse event.

In addition, if comparison between before and after the administration of the investigational product is assessed as a clinically significant change during the safety assessment such as vital signs, physical examinations, etc., it should be recorded in the adverse event section of the case record.

## 15.2. Adverse Events

### 15.2.1. Definition of Adverse Events

1) Adverse Event (AE)

All harmful and unintended sign(s) (includes abnormal results, etc. of the laboratory tests), symptom(s), or disease(s) that occur to subjects receiving the investigational product which need not be causally related to the investigational product.

2) Adverse Drug Reaction (ADR)

All harmful and unintended reactions occurring at any dose of the investigational product, which cannot deny the causal relationship with the investigational product.

3) Unexpected Adverse Drug Reaction

Differences in the pattern or severity of abnormal drug reactions in light of available drug information, such as the investigator's brochure or support documents of the drug.

4) Serious Adverse Events/Adverse Drug Reaction

Any of the following adverse events or adverse drug reactions occurring at any dose of the investigational product

- In case of death or life-threatening cases
- In case where hospitalization is necessary or hospital stay needs to be extended
- In case of permanent or significant failure or degradation of function
- In case of malformations or abnormalities in the fetus

In addition to the circumstances listed above, if a situation occurs that would have a clinically significant impact on the health and well-being of the subjects, it should be determined whether or not the subject will be considered a serious adverse reaction, based on the medical judgment of the investigator and related professionals and proper measures should be taken.

However, in the case of the following subjects, it is not regarded as SAEs.

① Subject chooses hospitalization prior to the clinical study or hospitalization for planned treatment/surgical procedure and extension of the hospitalization period for the existing concurrent illness not worsened during the study period (admission to a rehabilitation institution from before taking the investigational product, admission to a nursing home, or a nursing home to inspect admission and laboratory performance abnormalities, if the subject is living far away from the hospital, or doesn't have a caregiver at home, etc.)

② Discharge within 24 hours after hospitalization (visit to the emergency room not causing hospitalization)

5) Special cases (pregnancy): Exposure to the investigational product during pregnancy

**15.2.2. Assessment Criteria**

The investigator will assess adverse events according to the following criteria for severity and causal relationship.

Assessment of severity

The severity of an adverse event is indicative of the severity of the condition and should be assessed separately from the severity of life-threatening, functional decline, or condition requiring treatment. The severity is evaluated according to the following criteria:

- Mild: Showing symptoms or signs but without hindrance to daily life
- Moderate: The degree to which routine activities are restricted and sufficiently inconvenienced
- Severe: To the extent that daily activities cannot be carried out

2) Assessment of the causal relationship with investigational product

The investigator evaluates the causal relationship between the investigational product and the adverse event on the basis of the following criteria. And all adverse events are considered adverse drug reactions unless evaluated as "probably not related" or "definitely not related."

① Definitely related

- If there is evidence that the investigational product has been administered and the time sequence of adverse events is reasonable
- If the adverse event is most likely explained by the administration of the investigational product more than any other reasons
- If adverse events disappear as a result of discontinuation of administration
- If re-administration (only if possible) result is positive
- If the adverse event is consistent with information already known about the investigational product or the same type of drug

② Probably related

- If there is evidence that the investigational product has been administered and the time sequence of adverse events is reasonable
- If the adverse event is most likely explained by the administration of the investigational product more than any other reasons
- If adverse events disappear as a result of discontinuation of administration (only if performed)

③ Possibly related

- If there is evidence that the investigational product has been administered and the time sequence of adverse events is reasonable
- If the adverse event is believed to be due to the administration of the investigational product at the same level as other potential causes
- If adverse events disappear as a result of discontinuation of administration (only if performed)

④ Probably not related, Unlikely

- If there is evidence of administering the investigational product
- If there are other more likely causes for the adverse event
- If suspension of administration (if performed) result is negative or unknown

- If re-administration (if performed) result is negative or unknown

⑤ Definitely not related; None
- If the subject has not received the investigational product
- If the time sequence between the administration of the investigational product and the development of the adverse event is not feasible
- If there is another obvious cause for an adverse event

⑥ Unknown, Unassessable
- If information cannot be judged because it is insufficient or conflicting and cannot be supplemented or verified.

**15.2.3. Reporting of Adverse Events**

Adverse events are those in which unexplained symptoms that appeared before the administration of the investigational product, either during the period of administration, or before the administration of the investigational product, and increased during the treatment period, regardless of the causality with the investigational product (including abnormal levels in clinical pathology), symptoms or illnesses, etc.

Adverse events should be monitored until the time of recovery to the status before treatment with the investigational product or the reference value, or until the investigator can determine that the adverse event has become normal or until further observation is deemed unnecessary. However, any new signs or symptoms that occur 30 days after the last administration of the investigational product will not be considered as adverse events.
Information on adverse events detected by the investigator during scheduled or unscheduled visits during the period of collection of adverse events should be recorded in the case record form, and the information to be collected is as follows:

- Name of adverse events (including the start date/date of disappearance, etc.)
- Assessment of severity (See Section 1 of 15.2.2)
- Causal relationship with the investigational product (See Section 2) of 15.2.2)
- Seriousness
- Actions taken for investigational product
- Measures made to treat the adverse event

**15.2.4. Reporting Methods of Serious Adverse Events**

The principal- and sub-investigators should notify Daewoong Pharmaceutical Co., Ltd. of all SAEs occurring during the treatment period of the investigational product within 24 hours after coming to know about them or by the following working day at the latest (based on business days) regardless of the causal relationship with the investigational product by phone or fax (Phone: 02-550-8800, FAX: 02-550-8444) or report to the contract research organization (relevant monitoring staff). And, the report should also be made to the IRB according to the safety reporting procedures of each study site.

Where possible, the initial report should include all items on the SAE Form and all completed forms should be sent to the sponsor. The investigator should complete the adverse event page of the case record form, in addition to the SAE Form. If necessary, a follow-up report containing all new information on SAEs should be completed on the SAE Form and sent to the sponsor.

After receiving the initial report, the sponsor and the IRB should review the information and, if

necessary, contact the investigator for further information. After reviewing the information on adverse events, the causal relationship with the investigational product should be investigated.

The sponsor will report to the Minister of Ministry of Food and Drug Safety within the following time period if serious or unexpected adverse drug reaction occurs:

- If it causes death or life-threatening: Within 7 days from the date on which the sponsor was notified of or learned the relevant fact. In this case, detailed information on adverse drug reactions should also be reported within 8 days of the initial reporting date.
- For all other serious and unexpected adverse drug reactions: It should be reported within 15 days from the date on which the sponsor was notified of or learned about the relevant fact.

The investigator is responsible for reporting special cases (if pregnant) even if they do not correspond to a SAE. The investigator instructs female subjects to notify him/her immediately if she becomes pregnant during the study period If female subjects become pregnant after taking the investigational product, the investigator will promptly report all pregnancies (within 24 hours of occurrence) according to the SAE reporting method, even if no adverse events occur. In addition, pregnancy is not considered to be a SAE/ADR, but they should be dropped out from the study. And, the progress of pregnant women and fetuses should be tracked and reported until 30 days after delivery.

## 16. Informed Consent form, Compensation Rules, and Diagnosis and Treatment of Subjects after Study

### 16.1. Informed Consent Form for Subjects

The principal-/sub-investigators will fully explain to the subject the purpose and method of the study, the effect and adverse events of the investigational product in advance and obtain an informed consent from the subject.

Appendix 4. See the Informed Consent Form for Subjects

### 16.2. Compensation Rules for Victims

Appendix 5. See the Compensation Rules for Victims

### 16.3. Diagnosis and Treatment of Subjects

Subjects who are dropped out of the study or who show no therapeutic effect should be given other proper treatment. Subjects who have completed the study should select the best treatment method according to the investigator's judgment.

## 17. Measures to Protect the Safety of Subjects

This study will be conducted scientifically and ethically in accordance with the KGCP and the relevant laws and regulations related to clinical studies. In addition, this study will be conducted in accordance with the Declaration of Helsinki in order to respect human dignity and rights, and to prevent disadvantages to the subjects.

The study site conducting the study should be equipped with facilities and the professional staff necessary for carrying out the study and should be ready to carry out the study appropriately.

The IRB will evaluate and approve the protocol in accordance with the GCP and will periodically evaluate whether the study is proceeding according to the protocol.

The investigators should thoroughly confirm that the subjects are healthy enough to participate in the study by checking the health status of each subject before they are enrolled in the study. In addition, the investigator should be fully familiar with the protocol and the investigational product, and carry out the study according to the protocol. He/she will do their best to ensure the safety of the subjects, and if adverse events occur due to the study, appropriate medical actions should be taken until the patient recovers.
If the subject wishes to be treated due to an adverse event during the study period or if the investigator considers that medical treatment is necessary, he/she should immediately visit the study site conducting the study and receive relevant tests such as blood pressure measurement, laboratory tests, etc. If the investigator judges that the study should be stopped by evaluating the adverse events and the test results, or if the subject wants to discontinue the study, the investigator should promptly proceed with the procedure according to the termination of the study and actively carry out the treatment that can alleviate the corresponding symptoms of the subject.

## 18. Other Requirements for Safe and Scientific Implementation of Study

### 18.1. Good Clinical Practice (GCP, ICH E6)

The procedures set out in this protocol are designed to ensure that the sponsor and the investigator comply with the essential spirit of the Good Clinical Practices (KGCP, ICH E6) and the Declaration of Helsinki in conducting and evaluating this study and documenting the results.

### 18.2. Subject's Consent

The investigator should explain the nature, scope, and expected results of the study to the participants of the clinical study in advance using their native language (mother tongue) so that they can easily understand. The investigator should ensure that the subject is free to decide their participation in the study and that he/she has a clear understanding that he/she can refuse to participate in the study without any damage or loss of profits or that he/she can stop at any time during the study.

The subject shall have time to fully consider the participation in the study after hearing the explanation about the study and can fully discuss with the family or acquaintances. The subject shall also be able to request explanations from the investigator at any time and receive satisfactory answers if he/she does not understand any part of the study.

The investigator shall obtain the consent from the subject in writing, and the informed consent form will be signed and dated by the investigator and the subject by hand. The original copy of the signed informed consent form must be kept by the investigator, and a copy must be given to the subject.

By signing the informed consent form, the subject agrees to participating in the clinical study, and the collection and use of the subject's personal information in connection with the clinical study. The personal information of the subject is used to identify the subject and to connect the clinical information collected during the clinical study process. The collected personal information is coded so that the individual's identity cannot be known and cannot used directly as clinical study data.

The scope of personal information collected in relation to the clinical study includes personal identification information (name, contact information, etc.), demographics, medical records (past medical history, treatment history, etc.), and results of tests performed in relation to the clinical study. All collected data should be treated in accordance with the laws, rules and regulations on the

protection of personal privacy.

The investigator should not carry out any tests for the clinical study before obtaining a consent from the subject.

### 18.3. Institutional Review Board (IRB)

Before commencing clinical study, the investigator should be reviewed by the IRB for the investigator's brochure, clinical study protocol, informed consent form for subjects, method of recruiting subjects (including advertisements, etc.), and other information provided in writing to the subject. The IRB will send the results of the review for conducting the study to the sponsor and the investigator in writing prior to the commencement of the clinical study.

The principal investigator should conduct a clinical study after obtaining the IRB's approval of the clinical study protocol and any revisions or changes. In addition, events that may affect the safety of the patient including SAEs or the continued performance of clinical study, especially safety-related changes, must be reported to the IRB. A report on the progress should be submitted to the IRB once a year, and when the clinical study is completed, it should be notified to the IRB.

### 18.4. Monitoring and Inspection of Compliance with the Protocol

To ensure that the rights and welfare of the subjects are protected, verify the accuracy, completeness and verifiability of the data, and check that the clinical study is conducted according to the protocol and KGCP approved by the Minister of Ministry of Food and Drug Safety and IRB, monitoring planned by the sponsor will be performed.

A monitoring agent from the sponsor side will visit the study site conducting the study to check completeness and clarity of a case record form, compare with the base data, and conduct verification, etc. of the managerial task. And, the investigators should cooperated with this. During the monitoring visit, the monitoring personnel will review the informed consent form for subjects, patient recruitment and follow-up monitoring, recording and reporting of serious adverse events, distribution of investigational products, patients' compliance with the use and dose of investigational products, amount of investigational products, concomitant treatment, quality of data, etc. with the investigators.

The sponsor may conduct an audit as part of a credibility assurance and verify that the clinical study has been carried out in accordance with the protocol, SOP and relevant regulations. In addition, the Minister of Ministry of Food and Drug Safety can check whether the study was conducted according to the GCP and related regulations through the inspection. If reading study-related documents for monitoring or inspection is requested by the sponsor or officials of MFDS, the principal investigator or the head of study site should cooperate with this actively.

### 18.5. Confidentiality

All records that identify the subject should remain confidential. All documents related to clinical study such as case record forms should be recorded and identified with the subject identification code (subject number, initial), not the name of the subject. If there is a subject's name on documents provided to the sponsor (pathological report, medical imaging record, etc.) among medical records, it should be deleted before being provided to the sponsor.

The sponsor (monitoring personnel, etc.), IRB, and MFDS can read medical records of the subjects for the purpose of identifying the information collected, and the information exposed when they are read will be handled with utter confidentiality. And, the investigator will notify the subject of this.

### 18.6. Archiving Data

The investigator will take measures to prevent accidental or premature destruction of all documents related to the clinical study. It is recommended that the clinical study-related documents are retained for at least three years from the date of termination of the study after the completion or discontinuation of this study or the date of product license. The investigator should notify the sponsor in advance of the destruction of documents required for the study after the completion or discontinuation of the study. If the investigator can no longer keep the documents, he/she should inform the sponsor so that the related documents can be sent to the mutually agreed representative.

### 18.7. Policy on Submission and Publication of Report

By signing this study protocol, the investigators agree to use the results of this study for registration, publication, and provision of information to medical practitioners. The sponsor has a right to review all summaries, manuscripts or presentations related to this study before publishing them in academic journals. The investigators will not make any publications or academic presentations related to the clinical study results without prior agreement from the sponsor in writing and will be responsible for not disclosing this information to a third party. The sponsor has the right to publish the results of this clinical study at any time.

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## Appendix 1. ECOG Performance Status Scale*

| Grade | Status |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair |
| 5 | Dead |

* As published in Am. J. Clin. Oncol.:
Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP., Toxicity and response criteria of the eastern cooperative oncology group. Am J Clin Oncol. 1982; 5(6):649-55.

## Appendix 2. Questionnaire for Evaluation of Symptoms of Biliary Reflux

The following questions list five (or six) answers about how often the following gastrointestinal symptoms occurred over the past two weeks, how severe the symptoms were, and how much you suffered. Please mark those that apply with o in a number.

| | **How often** did it occur?<br>0 = None.<br>1 = 1 to 4 days<br>2 = 5 to 8 days<br>3 = 9 to 12 days<br>4 = Every day, almost every day | How severe were the symptoms?<br>0 = None.<br>1 = Very weak.<br>2 = Weak.<br>3 = Somewhat severe.<br>4 = Severe.<br>5 = Very severe. | How **bad** were the symptoms?<br>0 = None.<br>1 = Very weak.<br>2 = Weak.<br>3 = Severe.<br>4 = Very severe. |
|---|---|---|---|
| 1. Pain in the upper abdomen<br>(If it hurts or feels stiff.) | 0 1 2 3 4 | 0 1 2 3 4 5 | 0 1 2 3 4 |
| 2. Heartburn<br>(Stinging or burning sensation) | 0 1 2 3 4 | 0 1 2 3 4 5 | 0 1 2 3 4 |
| 3. (Nausea, discomfort) | 0 1 2 3 4 | 0 1 2 3 4 5 | 0 1 2 3 4 |

## Appendix 3. Expected Side Effects and Precautions for Use

Expected side effects of DWJ1319 and precautions for use are based on the approval of Ursa-D Capsule 300 mg.

1. It should not be given to the following patients:
1) Patients with hypersensitivity to this component or bile acid
2) Patients with severe biliary obstruction (may worsen the symptoms because of the choleretic action)
3) Patients with fulminant hepatitis (may worsen the symptoms)
4) Patients with calcified cholesterol gallstones or patients with radiation-impermeable gallstones or bile pigment gallstone
5) Patient with non-functional gallbladder
6) Patients requiring cholecystectomy due to continuous acute cholecystitis, cholangitis, biliary obstruction, gallstone pancreatitis, and biliary gastrointestinal tract fissura
7) Women who are pregnant or who may be pregnant and breast feeding women
8) Children
9) Patients with a kidney disease
10) Patients with peptic ulcer (acute gastric or duodenal ulcer) (may worsen the symptoms due to mucous membrane irritation)
11) Patients with colitis and enteritis such as Crohn's disease

2. Caution will be taken when giving it to the following patients:
1) Patients with severe pancreatic disease (can worsen the original disease)
2) Patients with gallstones in the bile ducts (may cause cholestasis because of the choleretic action.)
3) Patients with varicose vein bleeding, hepatic coma, ascites, and who suddenly require a liver transplantation

3. Adverse events
The nature and frequency of adverse events were similar in all groups.
The table below is a comprehensive table of adverse events reported with an incidence of 5% or more.

| | **Dissolution of gallstone** | | | |
|---|---|---|---|---|
| | Ursodeoxycholic acid 8-10 mg/kg/day (n = 155) | | Placebo (n = 159) | |
| **Whole body** | N | (%) | N | (%) |
| Allergy | 8 | (5.2) | 7 | (4.4) |
| Chest pain | 5 | (3.2) | 10 | (6.3) |
| Fatigue | 7 | (4.5) | 8 | (5.0) |
| Virus infection | 30 | (19.4) | 41 | (25.8) |
| **Digestive system** | | | | |
| Abdominal pain | 67 | (43.2) | 70 | (44.0) |
| Cholecystitis | 8 | (5.2) | 7 | (4.4) |
| Constipation | 15 | (9.7) | 14 | (8.8) |
| Diarrhea | 42 | (27.1) | 34 | (21.4) |
| Indigestion | 26 | (16.8) | 18 | (11.3) |
| Flatulence | 12 | (7.7) | 12 | (7.5) |

| | | | | |
|---|---|---|---|---|
| Gastrointestinal disturbance | 6 | (3.9) | 8 | (5.0) |
| Nausea | 22 | (14.2) | 27 | (17.0) |
| Vomiting | 15 | (9.7) | 11 | (6.9) |
| **Musculoskeletal system** | | | | |
| Arthralgia | 12 | (7.7) | 24 | (15.1) |
| Arthritis | 9 | (5.8) | 4 | (2.5) |
| Back pain | 11 | (7.1) | 18 | (11.3) |
| Myalgia | 9 | (5.8) | 9 | (5.7) |
| **Nervous system** | | | | |
| Headache | 28 | (18.1) | 34 | (21.4) |
| Insomnia | 3 | (1.9) | 8 | (5.0) |
| **Respiratory system** | | | | |
| Bronchitis | 10 | (6.5) | 6 | (3.8) |
| Cough | 11 | (7.1) | 7 | (4.4) |
| Pharyngitis | 13 | (8.4) | 5 | (3.1) |
| Rhinitis | 8 | (5.2) | 11 | (6.9) |
| Nasosinusitis | 17 | (11.0) | 18 | (11.3) |
| Upper respiratory tract infection | 24 | (15.5) | 21 | (13.2) |
| **Genitourinary system** | | | | |
| Urethral infection | 10 | (6.5) | 7 | (4.4) |

**Gallstone prevention**

| | Ursodeoxycholic acid 600 mg (n = 322) | | Placebo (n = 325) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| **Whole body** | | | | |
| Fatigue | 25 | (7.8) | 33 | (10.2) |
| Virus infection | 29 | (9.0) | 29 | (8.9) |
| Influenza-like symptoms | 21 | (6.5) | 19 | (5.8) |
| **Digestive system** | | | | |
| Abdominal pain | 20 | (6.2) | 39 | (12.0) |
| Constipation | 85 | (26.4) | 72 | (22.2) |
| Diarrhea | 81 | (25.2) | 68 | (20.9) |
| Flatulence | 15 | (4.7) | 24 | (7.4) |
| Nausea | 56 | (17.4) | 43 | (13.2) |
| Vomiting | 44 | (13.7) | 44 | (13.5) |
| **Musculoskeletal system** | | | | |
| Back pain | 38 | (11.8) | 21 | (6.5) |
| Musculoskeletal pain | 19 | (5.9) | 15 | (4.6) |

| | | | | |
|---|---|---|---|---|
| **Nervous system** | | | | |
| Dizziness | 53 | (16.5) | 42 | (12.9) |
| Headache | 80 | (24.8) | 78 | (24.0) |
| **Respiratory system** | | | | |
| Pharyngitis | 10 | (3.1) | 19 | (5.8) |
| Nasosinusitis | 17 | (5.3) | 18 | (5.5) |
| Upper respiratory tract infection | 40 | (12.4) | 35 | (10.8) |
| **Skin and other organs** | | | | |
| Hair loss | 17 | (5.3) | 8 | (2.5) |
| **Genitourinary system** | | | | |
| Menstrual pain | 18 | (5.6) | 19 | (5.8) |

In addition to the above table, the following adverse events may occur:

1) Interstitial pneumonia: If interstitial pneumonia is accompanied by fever, cough, dyspnea, or an abnormal chest X-ray appears, discontinue administration and take appropriate actions.
2) Others: In rare cases, systemic malaise, dizziness, calcification of gallstones, elevated liver enzymes (ALT, ALP, AST, γ-GT) and leucopenia may occur.
3) If there is a rise in serum bilirubin, administration should be stopped, and proper measures should be taken.

4. General cautions

1) When given to patients with high jaundice in the liver cirrhosis, symptoms may worsen, so it should be administered carefully.
2) Hepatic enzyme values of the plasma (ALT, ALP, AST, γ-GT, total bilirubin) should be examined regularly during the treatment.
3) Severe adverse events due to overdose are unlikely to occur, but liver function tests should be performed if necessary.

5. Interaction

1) There is a risk of increasing the action of the following drugs: Oral diabetic agent (tolbutamide)
2) The following drugs may interfere with the absorption of this drug and reduce the effect of the drug.
   : Antacids containing cholestyramine, colestipol, medicinal charcoal, magnesium and aluminum hydroxide
3) Drugs that increase cholesterol secretion in the liver (e.g., oral contraceptives containing estrogen and lipid-lowering drugs such as clofibrate) may weaken the action of this drug because they promote cholesterol gallstone formation.
4) Concomitant use with drugs that damage the liver should be avoided.

6. Administration to pregnant women and breast feeding women, children and the elderly

1) Pregnant women
   Studies on reproductive toxicity were performed in rats and rabbits up to 200 times the treatment dose of this drug, and no evidence of damage to the fetus or reproductive capacity was found in rats at 20-100 times the dose of the human dose. In rabbits, such evidence was not found at five times the human dose. Studies in which rats were given 100-200 times the human dose showed some reductions in fertility and the number of embryos born in the same womb. No adequate and well-controlled clinical study has been performed in pregnant women. However, during the clinical study period of this drug, there was no effects on the fetuses or newborns of 4 women who were unintentionally treated with a treatment dose during the first 3

months of pregnancy. This drug is not considered to cause damage to the fetus, but it is not recommended to take this drug during pregnancy, as such possibility cannot be excluded.

2) Breast feeding women
It is not known whether this drug is excreted through human milk. Because many medications are excreted through human milk, it is not recommended to give this drug to breast feeding women.

3) Children
The safety and efficacy of this drug in pediatric patients has not been established.

4) Elderly
Approximately 14% of the subjects who participated in the multinational clinical study of this drug were 65 years or older (3% were over 75 years or older). A sub-analysis conducted of the clinical studies that have been completed to date shows no statistically significant difference in complete gallstone dissolution rate when patients of 56 years or older are compared to younger patients. There were no age-related differences in safety and efficacy. Reports on other clinical experiences also showed no difference in the response between elderly and young patients. However, the possibility of a small difference in efficacy or sensitive reaction in some elderly patients who received this drug cannot be excluded. Therefore, caution is advised when administering it to the elderly.

7. Treatment for overdose

No accidental or intentional overdose has been reported. Seven patients who received in a dose range of 16-20 mg/kg/day had no symptoms for 6-37 months and had no tolerability problems. In rats, the $LD_{50}$ of this drug was 5,000 mg/kg for 7-10 days and 7,500 mg/kg in mice. The symptom that is likely to occur in case of a significant overdose of this drug is expected to be diarrhea, and it should be treated.

8. Precautions for storage

1) Keep out of reach of children.
2) Removing medication(s) from their original containers and storing them in other containers may cause accidents due to misuse of medication(s) or deterioration of the quality of medication(s). Thus, they should be put in original containers and kept tightly closed.

# Statistical Analysis Plan

**Protocol No.: DW_UDCA005**

**Efficacy and Safety of DWJ1319 in the Prevention of Gallstone Formation after Gastrectomy in Patient with Gastric Cancer: A Multicenter, Randomized, Double-blind, Placebo-controlled Study**

**Sponsor: Daewoong Pharmaceutical Co., Ltd.**

**Author: Park, Su Jin**

**Protocol Version: DW_UDCA005_v2.3, 2016-02-23**

**SAP Version: SAP_ DW_UDCA005_v1.0, 2018-06-20**

## English Translation Version

## Signature Page

**Not Applicable**(English Translation Version)

# History of Revision

| | | | |
|---|---|---|---|
| **Protocol No.** | DW_UDCA005 | **Sponsor** | Daewoong Pharmaceutical Co., Ltd. |
| | | **CRO** | LSK Global PS |
| **Approval Date** | **Amended Version** | **Reason** | |
| NA | | | |

# List of Contents

# 1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ALP | Alkaline Phosphatase |
| ALT(=SGPT) | Alanine Transaminase |
| ANCOVA | Analysis of Covariance |
| ANOVA | Analysis of Variance |
| AST(=SGOT) | Aspartate Transaminase |
| BMI | Body Mass Index |
| BUN | Blood Urea Nitrogen |
| CT | Computed tomography |
| CS | Clinically Significant |
| ECOG | Eastern Cooperative Oncology Group |
| eGFR | Estimated Glomerular Filtration Rate |
| FAS | Full Analysis Set |
| γ-GTP(=γ-GT) | Gamma-glutamyl transpeptidase (Gamma-glutamyl transferase) |
| Hb | Hemoglobin |
| Hct | Hematocrit |
| IWRS | Interactive Web Response System |
| LSM | Least-Square Mean |
| MedDRA | The Medical Dictionary for Regulatory Activities |
| NCS | Not Clinically Significant |
| PPS | Per-Protocol Set |
| PT | Preferred Term |
| RBC | Red Blood Cell |
| SAE | Serious Adverse Event |
| SE | Standard Error |
| SOC | System Organ Class |
| TEAE | Treatment-Emergent Adverse Event |
| UDCA | Ursodeoxycholic acid |
| WBC | White Blood Cell |
| WHO | World Health Organization |

## 2. INTRODUCTION

As domestic incidences of cancer continue to rise, gastric cancer is the second most common cancer accounting for 17.2% of total cancer incidences. In particular, it is the most common type of cancer in men, occurring more frequently than prostate cancer and colon cancer. Furthermore, due to early screening and the development of treatment techniques, the 5-year survival rate of patients with gastric cancer has been increasing every year. Therefore, there is a trend of decrease in complications for these patients due to treatment and a growing interest in improving their quality of life.

Currently, surgical treatment, chemotherapy, and radiation therapy are performed to treat gastric cancer. To date, surgical treatment is known to be the most fundamental and effective method for increasing the survival rate. Thus, the standard treatment for gastric cancer is surgery if a radical resection is possible. However, due to various causes such as anatomical changes after gastrectomy, major complications have been reported including alkaline reflux gastritis, reflux esophagitis, iron deficiency anemia, vitamin $B_{12}$ deficiency, metabolic bone disease, and cholelithiasis.

The proportion of patients with gallstone formation has been reported to be approximately 13%-17% within 1 year and 20% within 5 years after gastrectomy, and this is about 10% higher than the prevalence of gallstones in the general population (2.0% in Korea and 3.2% in Japan). The reason for the increased incidence of gallstones after gastrectomy is unclear. The predominant hypothesis is that the anatomical changes resulting from the surgery, especially in the event the vagus nerve is severed, affect contractility of the gallbladder, causing stasis and supersaturation of the bile that promote gallstone formation. In fact, the incidence of gallstones in patients who underwent pylorus-preserving gastrectomy is significantly low, supporting such hypothesis.

The gallstone prevention effect of UDCA, like the gallstone dissolution methods, are known to be manifested by suppressing supersaturation of cholesterol, which is a factor of gallstone formation, reducing nucleating factors, and improving gallbladder motility. The effect of oral administration of UDCA is an increase in bile reservoir and changes in bile acid composition, thereby suppressing the saturation of cholesterol through reducing cholesterol saturation in the gallbladder, intestinal cholesterol absorption, and cholesterol secretion in the bile. It has also been reported that it reduces nucleating factors such as glycoprotein in bile and improves gallbladder motility by affecting gallbladder contractility.

Since the gallstone prevention effect of UDCA is related to its inherent function as a tertiary bile acid, in addition to obese patients who have experienced rapid weight loss, it is expected to be effective in prevention of gallstone formation in patients with gastric cancer who underwent gastrectomy. However, to date, there has been no study on the effect of UDCA on the prevention of gallstone formation after gastrectomy for patients with gastric cancer. Therefore, Daewoong Pharmaceutical Co., Ltd. developed DWJ1319 with UDCA 300 mg as the active substance and planned a phase 3 clinical study to evaluate the efficacy and safety of DWJ1319 for the prevention of gallstone formation in patients with gastric cancer who underwent gastrectomy.

# 3. STUDY OBJECTIVES

## 3.1 Primary Objective

To assess the efficacy of DWJ1319 300 mg or DWJ1319 600 mg administered once daily for 52 weeks in the prevention of gallstone formation after gastrectomy in patients with gastric cancer compared with placebo.

## 3.2 Secondary Objective

To assess the safety and tolerability of DWJ1319 300 mg or DWJ1319 600 mg administered once daily for 52 weeks compared with placebo.

# 4. INVESTIGATIONAL PLAN

## 4.1 Overall Study Design and Plan

A multi-centered, randomized, double-blind, placebo-controlled, phase 3 clinical study. The subjects are patients who have been diagnosed with gastric cancer and underwent gastrectomy for treatment. Screening will be conducted on subjects who gave an informed consent to participate in the clinical study. Subjects who meet the inclusion criteria and do not meet exclusion criteria will be randomly assigned to DWJ1319 300 mg (DWJ1319 300 mg, once a day), DWJ1319 600 mg (DWJ1319 300 mg, twice a day), or placebo (1: 1: 1). For randomization, stratified randomization using the study site, the lymph node resection range (D1+, D2), and the type of gastrectomy as the stratification factors will be performed and randomization will be performed within 2 weeks from gastrectomy. During the study period, the subjects will visit the study site at screening, randomization (Day 1) and at 3-month intervals after the administration of investigational product (at 3, 6, 9, and 12 months) to undergo protocol-specified tests and procedures at each visit. However, any subject with formation of gallstone confirmed during the treatment period will terminate the study at the time of confirmation.

| Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 |
|---|---|---|---|---|---|
| Until week -2 | Day 1 | 3 months±1 week | 6 months±1 week | 9 months±1 week | 12 months±1 week |
| Screening | Randomization | Treatment period | | | |

## 4.2 Study Duration

The overall duration of this study is expected to be about 20 months, however, there may be a change in the duration if a situation arises that may affect the progress of the clinical study such as difficulties in selecting the subjects.

Study duration for each subject: About 54 weeks as follows.
• Screening period: 2 weeks
• Treatment period: 52 weeks (12 months)

## 4.3 Dosage, Administration and Schedule

All randomly assigned subjects are orally administered with the investigational product twice a day, one capsule at a time, for a total of 52 weeks. The subjects take the investigational product in the morning and evening according to the investigator's instructions and if possible, take it at the same time each day.

[Method of administration by treatment group]

| Treatment group | Method of administration | Study drug |
|---|---|---|
| Placebo | One capsule each of placebo for DWJ1319 in the morning and evening | Morning: ○, Evening: ○ |
| DWJ1319 300 mg | One capsule each of placebo for DWJ1319 in the morning and DWJ1319 in the evening | Morning: ○, Evening: ● |
| DWJ1319 600 mg | One capsule each of DWJ1319 in the morning and evening | Morning: ●, Evening: ● |

○: Placebo for DWJ1319, ●: DWJ1319

## 4.4 Randomization and Unblinding

### 4.4.1 Randomization

Randomization is performed to ensure the scientific validity of the clinical study, to reduce bias that may occur during the clinical study, and to prevent the investigator's subjectivity in assigning subjects to each treatment group.

Based on the stratification factors, stratified block randomization method is used to randomly assign subjects to DWJ1319 300 mg, DWJ1319 600 mg, and placebo at 1:1:1 ratio. This will be done by each study site conducting the clinical study using the SAS proc plan procedure.

Each stratification factor will be set with two levels as below:

- Lymph node resection range: D1+, D2
- Type of gastrectomy: Total gastrectomy, partial gastrectomy

The procedure for assigning test subjects to each treatment group and prescribing and distributing the investigational product is as follows:

When the subjects are enrolled on Day 1, the investigator assigns to each subject a randomization number based on the pre-generated randomization results, via the interactive web response system (IWRS). The investigator prescribes the investigational product using the randomization number and the pharmacist distributes the investigational product with the same assigned number to the subject.

The randomization number of a subject withdrawn from the study will also be withdrawn but retained. New subjects must be assigned new screening numbers and randomization numbers.

### 4.4.2 Unblinding

This clinical study maintains a blind on the type of drug assigned to each subject on the investigator and subject. By maintaining the double-blinding on both the investigator and subject, it allows the investigator or subject to avoid bias in assessing treatment effects and adverse reactions. The study drug and the comparator in this clinical study should be manufactured in the same form so that it cannot be visually distinguishable for the double-blinding. The sub-portion packaging should also be the same.

If it is deemed necessary to remove the blinding due to the occurrence of an emergency

situation that threatens the safety of the subject, the investigator should immediately notify Daewoong Pharmaceutical Co., Ltd. or the monitoring staff of the contract research organization delegated by Daewoong Pharmaceutical Co., Ltd. The monitoring staff is obliged to immediately contact the representative of Daewoong Pharmaceutical Co., Ltd. After obtaining the relevant information, the representative of Daewoong Pharmaceutical Co., Ltd. will discuss with the investigator to decide whether to remove the blinding and document the decision. After consulting with the sponsor, the investigator will access the unblinding screen of the randomization website, input necessary information, obtain information on the investigational product of the subject, print the screen, sign it, and keep it under the investigator's file.

In the event that it is impossible to immediately contact Daewoong Pharmaceutical Co., Ltd., the sponsor, the investigator will access the unblinding screen of the randomization website, input necessary information, obtain information on the investigational product of the subject, print the screen, sign it, and keep it under the investigator's file. In such case, the investigator must notify Daewoong Pharmaceutical Co., Ltd. as soon as possible of the unblinding of the double-blind, and document the reasons for unblinding without consulting the sponsor.

If the investigator finds out the subject's code during the study, the investigator should endeavor to eliminate bias in assessing efficacy and safety.

After completing the study, the investigator will resolve any issues on all data through the Data Clarification Form (DCF). Once the database is confirmed to be complete and accurate, the data will be locked and randomization code information will be released. Subsequent changes to the database are possible only with the written consent of the sponsor and the database administrator.

## 4.5 Schedule of Study

The clinical study is conducted according to the following schedule.

| | **Screening** | **Baseline** | **Treatment** | | | |
|---|---|---|---|---|---|---|
| | **Visit 1** | **Visit 2** | **Visit 3** | **Visit 4** | **Visit 5** | **Visit 6 / Early termination[1)]** |
| **Duration** | From Week - 2 Day - 1 | Day 1 | Month 3 (±1 week) | Month 6 (±1 week) | Month 9 (±1 week) | Month 12 (±1 week) |
| Informed consent[2)] | ○ | | | | | |
| Demographic survey | ○ | | ○[3)] | ○[3)] | ○[3)] | ○[3)] |
| Medical history/prior surgery | ○ | ○ | | | | |
| Physical examination | ○ | | | ○ | | ○ |
| Vital signs | ○ | ○ | ○ | ○ | ○ | ○ |
| Inclusion/exclusion criteria | ○ | ○ | | | | |
| Randomization | | ○ | | | | |
| Abdominal ultrasound[4)] | ○[5)] | | ○ | ○ | ○ | ○ |

| | Screening | Baseline | Treatment | | | |
|---|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 | Visit 6 / Early termination[1)] |
| Duration | From Week - 2 Day - 1 | Day 1 | Month 3 (±1 week) | Month 6 (±1 week) | Month 9 (±1 week) | Month 12 (±1 week) |
| Abdominal CT scan[6)] | ○[5)] | | | ○ | | ○ |
| Assessment of bile reflux symptoms | | ○ | ○ | ○ | ○ | ○ |
| Upper gastrointestinal endoscopy[6)] | | | ○ | | | ○ |
| Laboratory tests | ○[7)] | | ○[8)] | ○ | ○[8)] | ○ |
| Pregnancy test[9)] | ○ | | | | | |
| Prescription of investigational product | | ○ | ○ | ○ | ○ | |
| Treatment compliance | | | ○ | ○ | ○ | ○ |
| Adverse events | | | ○ | ○ | ○ | ○ |
| Prior/concomitant medications[10)] | ○ | ○ | ○ | ○ | ○ | ○ |

1) For a withdrawal or early termination, the procedures for Visit 6 will be performed.
2) The informed consent form will be obtained in writing prior to study initiation after explaining the objectives and details of the study to the subjects. The informed consent should be obtained prior to any study procedures.
3) At the screening visit, the demographics (subject initials, sex, date of birth, smoking status and alcohol use, weight, height, BMI, etc.) will be collected. Thereafter, only weight will be measured at each visit.
4) The measuring will be conducted in a fasted state (including the investigational product) on the day of visit. If not in a fasted state on the day of visit, the subject will revisit within the imaging test window (regular visit ± 2 weeks) to carry out the examination. A subject with confirmed gallstone formation during the study period will terminate the study at the time of confirmation.
5) If there is a recent imaging test result (within 6 weeks before screening), the result can be used as a screening test result.
6) Abdominal CT and upper gastrointestinal endoscopy (once every 3 months or 12 months) are routine tests that are usually performed in association with gastrectomy. If there is a result of such tests, the results of the routine tests are collected and used without performing additional testing.
7) For any screening test result not meeting the inclusion/exclusion criteria, only one re-test is allowed.
8) At Visits 3 and 5, Liver function tests (ALT, AST, ALP, γ-GTP, and total bilirubin) among laboratory tests will be performed.
9) Urine HCG test will be performed only in women of childbearing age and the result should be confirmed prior to the administration of the investigational product.
10) Any drug that has been administered from 4 weeks before the screening visit throughout the study or is currently administered should be recorded.

## 4.6 Determination of the Sample Size

1) Number of Subjects to be Recruited

Taking into account the 20% withdrawal rate, this clinical study plans to enroll a total of 519 subjects (173 per group).

2) Calculation Basis

The primary objective of this study is to assess the efficacy of the study drug compared with placebo in preventing gallstone formation after gastrectomy in patients with gastric cancer. If the efficacy of DWJ1319 300 mg or 600 mg versus placebo is statistically significant, the study drug is considered to demonstrate its superiority. The endpoint is the percentage of subjects forming gallstones within 12 months of gastrectomy. The hypothesis to test this is as follows:

$H_0$ (Null hypothesis): $P_{T1} = P_C$ and $P_{T2} = P_C$
$H_1$ (Alternative hypothesis): $P_{T1} \neq P_C$ or $P_{T2} \neq P_C$

$P_{T1}$: Proportion of subjects forming gallstones after taking 600 mg of DWJ1319
$P_{T2}$: Proportion of subjects forming gallstones after taking 300 mg of DWJ1319
$P_C$: Proportion of subjects forming gallstones after taking placebo

For testing of each treatment group versus the placebo, the significance level of the test is not corrected because a sequential multiple test (twice) is performed using the fixed sequece method. The test sequence is 600 mg of DWJ1319 versus placebo and 300 mg of DWJ1319 versus placebo.

The following results were referenced to calculate the number of subjects to be tested.

| | Placebo | Ursodiol 300 mg | Ursodiol 600 mg | Ursodiol 1,200 mg |
|---|---|---|---|---|
| Study 1 (6M) | 32.14% (18/56) | 13.21% (7/53) | 1.64% (1/61) | 6.35% (4/63) |
| Study 2 (12M) | 16.94% (112/661) | - | - | - |
| Study 3 (12M) | 13.64% (6/44) | - | - | - |

In this clinical study, the incidence of gallstones with placebo was estimated to be 18%, which is the weighted average of study 1, 2 and 3, where study 1 is the result of placebo in obese patients who underwent gastrectomy and studies 2 and 3 are the adjusted results of placebo in patients with gastric cancer who underwent gastrectomy. Since it is difficult to estimate the incidence of gallstone of DWJ1319 by each dose, 7%, which is the weighted average of the three Ursodiol treatment groups in study 1, was estimated as the rate of gallstone formation for the study drug.

In addition to the above assumptions, the significance level is 5% for two-sided test, 80% for test power, and the minimum number of subjects for 1:1:1 assignment is as follows.

$$N = \frac{\left(Z_{1-2/\alpha} + Z_{1-\beta}\right)^2 \{P_T(1-P_T) + P_C(1-P_C)\}}{\delta^2}$$

$$= \frac{(1.96 + 0.842)^2 \{0.07(1-0.07) + 0.18(1-0.18)\}}{(0.07-0.18)^2} \approx 138$$

The minimum number of subjects required to have a power level of 80% at the 5% significance level is calculated as 138 per group. Taking into account the 20% withdrawal rate, this clinical study plans to enroll 173 people per group (total of 519).

# 5. ANALYSIS SETS

The validity data obtained from the subjects of this clinical study are analyzed in two forms, Full Analysis Set (FAS) and Per Protocol Set (PPS). Data on efficacy is analyzed using both FAS and PPS, and the final determination of efficacy endpoints is done by FAS analysis. Safety assessment is conducted on safety set.

## 5.1 Screened Set

It includes all subjects who have signed an informed consent and have been given a screening number.

## 5.2 Randomized Set

It includes all subjects randomized to the treatment groups.

## 5.3 Full Analysis Set (FAS)

Of the subjects which were administered the investigational product at least once after being randomized, the assessment will be conducted on those subjects that did not violate the inclusion/exclusion criteria, and had at least one evaluation for gallstone formation after randomization.

## 5.4 Per-Protocol Set (PPS)

The PP analysis set is composed of subjects who have completed the test without any serious deviation of the protocol that could affect the efficacy of the FAS analysis set. The subjects to be terminated according to the early termination criteria of Protocol 13.2 are included in the PP analysis set. The subjects who are excluded from the PP analysis set due to other serious deviations will clarify and the reasons will be documented prior to unblinding.

[Protocol 13.2 Early Termination of Clinical Study]

Subjects who have been confirmed to have gallstone formation by abdominal ultrasound during the post-randomization study drug administration period should stop participating in the clinical study at the time of such confirmation and perform a final assessment according to the Visit 6/early termination schedule. The subjects who finished early according to the early termination criteria are considered to have completed the clinical study according to the protocol, not withdrawn.

## 5.5 Safety Set

It includes all subjects administered with the investigational product at least once after being randomized.

# 6. DOCUMENTATION OF VARIABLES

## 6.1 Efficacy Variables

### 6.1.1 Primary Endpoint

The primary efficacy endpoint of this study is the percentage of subjects with gallstone formation within 12 months of gastrectomy based on the external investigator's assessment. At such point, whether or not gallstones are formed is determined by adopting the assessment result agreed on by two or more of the three external investigators.

- Percentage of subjects with gallstone formation (%) = (Based on external investigator's assessment, the subjects who were identified as having gallstone formation in at least one of the following sites, gallbladder, bile duct, and intrahepatic bile duct, within 12 months after gastrectomy*/Number of subjects analyzed)*100

  * In the case of the subjects who are confirmed to have gallstones by the institutional reviewer and are terminated early from the clinical study, to be conservative, they are defined as subjects with gallstone formation regardless of the external investigator's assessment.

[Protocol 11.2.7 Determination of Gallstones]

The diagnosis of gallstone formation is based primarily on the results of abdominal ultrasound and is supplemented by abdominal CT scan results. If the results of the two tests differ, abdominal ultrasound result should be considered first for gallbladder gallstones, and both abdominal ultrasound and abdominal CT should be considered in the case of bile duct gallstones or intrahepatic bile duct gallstones. If only the abdominal CT scan result is available, utilize the available CT scan result for the diagnosis of gallstone formation.

If the following criteria are satisfied as a result of abdominal ultrasound, make a diagnosis as gallbladder gallstone. If any one of the criteria is not met or there is only hyperechoic shadow without posterior acoustic shadow, it is judged negative for gallstone formation.

1) Hyperechoic shadow (echo sign)
2) Posterior acoustic shadow
3) The movement of echo according to changes in body position (movement, gravitational dependence)

The bile duct gallstone is distinguished by abdominal ultrasound that shows a hyperechoic substance with posterior acoustic shadow or an enlargement of peripheral bile duct around the echo, and is determined by compiling the results of abdominal CT scans.

Gallstones should be distinguished from biliary sludge and should be determined to be biliary sludge if the following criteria are met:

1) Hypoechoic shadow without accompanying acoustic shadow

2) Moves according to changes in body position and has a characteristic to form a horizontal plane

The investigator will document in the case report form (CRF) the presence of gallstones, the presence of biliary sludge, and the location of gallstones (gallbladder, common bile duct, intrahepatic bile duct), size and number of gallstones.

### 6.1.2 Secondary Endpoints

The secondary efficacy endpoints of this study are as follows:

1) Percentage of subjects forming gallstones within 3, 6, 9, and 12 months from gastrectomy

- Percentage of subjects with gallstones formation (%) = (The subjects who were identified as having gallstone formation in at least one of the following sites, gallbladder, bile duct, and intrahepatic bile duct, within 3, 6, 9, and 12 months after gastrectomy/Number of subjects analyzed)*100

2) Percentage of subjects forming gallstone within 3, 6, and 9 months from gastrectomy as assessed by the external investigator

- Percentage of subjects with gallstone formation (%) = (Based on external investigator's assessment, the subjects who were identified as having gallstone formation in at least one of the following sites, gallbladder, bile duct, and intrahepatic bile duct, within 3, 6, and 9 months after gastrectomy/Number of subjects analyzed)*100

3) Percentage of subjects forming biliary sludge within 3, 6, 9, and 12 months from gastrectomy

- Percentage of subjects with biliary sludge formation (%) = (The subjects who were identified as having biliary sludge formation at least once within 3, 6, 9, and 12 months after gastrectomy/Number of subjects analyzed)*100

4) Time to gallstone formation

- The time to gallstone formation is calculated as the time until the early termination or completion after a gastrectomy, if the gallstone has been formed within 12 months resulting in early termination, or at 12 months resulting in completion. Subjects who do not form gallstones until the completion of the clinical study are treated as censoring and their time period until completion is calculated. If subjects are withdrawn within the 12 months after a gastrectomy, they are treated as censoring data and their time period until the withdrawal is calculated.

  * In the case of the subjects who are confirmed to have gallstones by the institutional

reviewer and are terminated early from the clinical study, to be conservative, they are defined as subjects with gallstone formation regardless of the external investigator's assessment.

- Time to Gallstone Formation

  - Status = 1, if gallstones were formed

    = 0 (censoring), if gallstones were not formed until last f/u

  - Duration (day) = [Study Completion/Early Termination or Study Completion/ Dropout date (censored), whichever occurs first – date of gastrectomy +1]

#### 6.1.3 Exploratory Endpoints

The exploratory efficacy endpoints of this study are as follows:

1) Change in the biliary reflux symptoms from baseline at 3, 6, 9, and 12 months

- Change from baseline at n month = value at n month – baseline, n=3,6,9,12

2) Percentage of subjects who experienced biliary reflux according to the upper gastrointestinal endoscopy at 3 and 12 months

- Percentage of subjects with biliary reflux occurrence (%) = (The subjects who experienced biliary reflux at Months 3 and 12 after gastrectomy/Number of subjects analyzed)*100

3) Percentage of subjects who showed significantly abnormal AST and ALT values at 6 and 12 months

- Percentage of subjects who were CS for result of AST/ALT (%) = (The subjects who showed significantly abnormal AST and ALT values at 6 and 12 months after gastrectomy/Number of subjects analyzed)*100

### 6.2 Medical History and Concurrent Disease

#### 6.2.1 Medical History

Medical history is defined as a medical condition currently not persisting out of all collected historical medical conditions including allergies.

#### 6.2.2 Concurrent Disease

*Concurrent disease is defined as a medical condition currently persisting out of all collected historical medical conditions including allergies.*

#### 6.2.3 Prior Surgery

Prior surgery is defined as all collected surgical operations except gastric cancer surgery.

## 6.3 Prior and Concomitant Medication

### 6.3.1 Prior Medication

Prior medication is defined as medication whose onset of administration is before taking the first dose of the investigational product.

### 6.3.2 Concomitant Medication

Concomitant medication is defined as a drug whose onset of administration is after taking the first dose of the investigational product. If the starting or ending date of the administration is incomplete and it is difficult to distinguish the prior/concomitant medication, it is regarded as concomitant medication. If the start date of the administration is after the end of the clinical study, then it is excluded from the concomitant medication.

## 6.4 Treatment Compliance

Treatment compliance of the investigational product provided to the subject is collected at 3, 6, 9, and 12 months.

Treatment compliance by visit and overall treatment compliance for the investigational product provided to the subject are as follows and are rounded to the nearest two decimal places. Treatment compliance by visit is presented only for the regular visits, and overall treatment compliance is based on all information including withdrawal visits before the end of the study. However, it does not include unscheduled visits after a withdrawal visit.

- Treatment compliance is calculated using the following formula:

$$\text{Treatment compliance (\%)} = \frac{\text{Quantity (cap) of the investigational product actually taken}}{\text{Quantity (cap) of investigational product to be taken}^{1)}} \times 100$$

[1)] Number of investigational product to be taken

[Treatment compliance by visit] Quantity (cap) of investigational product to be taken = (Prescription date of the investigational product for the visit / If last visit, last visit date** – Prior prescription date of the investigational product) * 2

[Overall treatment compliance] Quantity (cap) of investigational product to be taken = (Last visit** - First prescription date of the investigational product) * 2

** For withdrawn subjects, if only the investigational product is returned without withdrawal visit, apply the clinical study ending date/withdrawal date

## 6.5 SAFETY VARIABLES

### 6.5.1 Extent of Exposure

In terms of extent of exposure to the investigational product, the total dose (㎎), exposure period (days) and average daily dose (㎎/day) are calculated as follows:

- Total dose (㎎) = Quantity (cap) of the investigational product actually taken x 300 ㎎
- Exposure period (day) = Last visit** – First prescription day of the investigational product

  ** For withdrawn subjects, if only the investigational product is returned without withdrawal visit, apply the clinical study ending date/withdrawal date
- Average daily dose (㎎/day) = total dose (㎎) / exposure period (day)

### 6.5.2 Treatment-Emergent Adverse Events (TEAEs)

The treatment-emergent adverse events (TEAEs) of the adverse events collected during the clinical study are evaluated, and the TEAEs are as follows:

- Adverse events that occurred after the "first dose of the investigational product after randomization"
- Among the symptoms that preceded the "first dose of the investigational product after randomization", adverse events with worsened severity following the "first dose of the investigational product after randomization"

However, if the occurrence date of the adverse event is missing or incomplete and, it is unclear if it had occurred pre or post "dose of the investigational product after randomization", then the event is considered as a TEAE.

**[Severity of Adverse Events]**

1) Mild: Showing symptoms or signs but without hindrance to daily life
2) Moderate: The degree to which routine activities are restricted and sufficiently inconvenienced
3) Severe: To the extent that daily activities cannot be carried out

**[Relevance to Investigational Product]**

1) Definitely related
2) Probably related
3) Possibly related
4) Probably not related, Unlikely
5) Definitely not related, None
6) Unknown, Unassessable

### 6.5.3 Adverse Drug Reaction

TEAEs' causal relationship to the investigational product is defined in the following Adverse Drug Reactions (ADRs) categories: Definitely related, Probably related, Possibly related, and Unknown or Unassessable.

### 6.5.4 Serious Adverse Event

Serious Adverse Event (SAE) means one of the following adverse events or adverse drug reactions that occur at any dose of an investigational product.

- In case of death or life-threatening
- In case where hospitalization is necessary or hospital stay needs to be extended
- In case of permanent or significant failure or degradation of function
- In case of malformations or abnormalities in the fetus

### 6.5.5 Vital Signs

Vital signs (blood pressure, pulse) are measured at each visit. Pulse and blood pressure should be measured after the subject has been sitting for 5 minutes, and always on the same arm for evaluation.

### 6.5.6 Laboratory Data

Laboratory tests are carried out using the Central lab and are performed in a fasted state at Visits 1, 4 and 6 or at the time of early termination/withdrawal. If screening results do not meet the inclusion/exclusion criteria, they may be retested only once. Women of childbearing age are checked for possibility of pregnancy by taking the urine hCG test at Visit 1. In addition, if it is deemed necessary by the investigator's judgment, further testing is possible.

Laboratory test items are as follows.

| | |
|---|---|
| **Hematology** | WBC, RBC, Hemoglobin (Hb), Hematocrit (Hct), Platelet count, WBC differential count (Neutrophil, Lymphocyte, Monocyte, Eosinophils, Basophils) |
| **Biochemical test** | Glucose, Total protein, Albumin, Total cholesterol, Triglyceride, Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), gamma-glutamyl transferase (γ-GTP), Uric acid, Creatinine, sodium, potassium, chloride, calcium, HbA1c*, eGFR |
| **Urinalysis** | Bilirubin, urobilinogen, Blood, Glucose, pH, Protein, Specific Gravity |
| **Pregnancy test**** | Urine HCG |

* HbA1c: It is performed once during the screening and if there is a test result within the last 3 months, it can be replaced for the screening test.
**Pregnancy test: It is performed only for women of childbearing age.

In addition, only the liver function tests (ALT, AST, ALP, γ-GTP and total bilirubin) among the biochemical tests are performed at Visits 3 and 5.

### 6.5.7 Physical Examination

Physical examination is performed at Visits 1, 4 and 6 or at the time of early termination/withdrawal. The investigator will perform a physical examination on the subject through an interview, examination, palpation, and auscultation and write the results on the case record. Examination categories include general appearance, skin/mucosa, lymphatic system, head/neck, eye/ear/nose/throat, gastrointestinal, cardiovascular, respiratory, neurological and musculoskeletal systems. The symptoms due to the underlying disease (gastric cancer and gastrectomy) of the clinical study are not collected.

# 7. DISPOSITION AND PROTOCOL DEVIATIONS

## 7.1 Subject Disposition

For the screening set, the frequency of the subjects who participated in the clinical study and the subjects who were randomized are presented. The subjects who were eliminated from the screening and the reason for their elimination are presented with frequency and percentage. For the randomized set, the frequency and percentage of the subjects who were administered the investigational product and the subjects who were terminated early or withdrawn from the clinical study are presented. For the subjects who were withdrawn, the reasons for withdrawal are presented with frequency and percentage. Also, a list of the subjects who have been withdrawn is complied.

A summary of the data is presented in the following table, list, and figure.

- T. Study Disposition (Screened Set)
- T. Subject Disposition by Site (Screened set)
- L. Discontinued Subjects (Randomized Set)

## 7.2 Analysis Sets

For the randomized set, the frequency and percentage of the subjects included in FAS, PPS, and Safety Set are presented. The reason for the exclusion from each analysis set is presented with frequency and percentage. Also, a list of subjects included or excluded in the analysis set is complied.

A summary of the data is presented in the following table and list.

- T. Analysis Set (Randomized Set)
- L. Analysis Sets (Randomized Set)

## 7.3 Protocol Deviations

For the randomized set, the frequency, percentage and the number of occurrence of serious deviations from the protocol are presented and the list of subjects who experienced a major deviation of the protocol is compiled.

A summary of the data is presented in the following table and list.

- T. Major Protocol Deviation (Randomized Set)
- L. Major Protocol Deviation (Randomized Set)

# 8. EFFICACY EVALUATION

## 8.1 Demographic and Baseline Characteristics

For the FAS, demographic information and baseline characteristics are summarized by each treatment group. For continuous data, mean, standard deviation, median, minimum, and maximum values are presented. For categorical data, frequency and percentage are presented. The differences among the treatment groups will be compared using the ANOVA or a Kruskal–Wallis test according to the normality test results for continuous data, and the chi-square test or Fisher's exact test for categorical data.

**Demographics**

- Continuous variables: Age (year), Height (cm), Weight (kg), BMI ($kg/m^2$)
- Categorical variables: Sex (Male, Female), Smoking Status (Yes, No, Ex-smoker), Drinking Status (Yes, No, Ex-drinker)

**Baseline Characteristics**

- Continuous variables: Disease duration(month)
- Categorical variables: TNM stage (T: 1, 1a, 1b, 2, 3, 4, 4a, 4b, other / N: 0, 1, 2, 3, 3a, 3b, other / M: 0, 1, other), Stage (IA, IB, IIA, IIB, IIIA, IIIB, IIIC, IV), Gastrectomy type (Total gastrectomy, Distal gastrectomy, Proximal gastrectomy), Gastrotomy method (Open surgery, Laparoscopic surgery, Other), Lymph Nodes Resection Range (D1+, D), Stomach Reconstruction (Yes, No), Stomach Reconstruction type (Billoth I, Billoth II, Roux-en-Y, Other), Supportive anticancer treatments (Yes, No), Supportive anticancer treatments type (Chemotherapy, Radiotherapy, Other), ECOG performance status at screening (0,1)

  ➢ Disease duration (month)

  = (Randomization Date - Diagnosis date of Gastric Cancer +1) x 12/365.25

  In calculating the disease duration, if the month and/or day under the diagnosis day is noted UK, then it is replaced it with "01". If the year is noted "UK", then exclude it from the disease duration analysis.

A summary of the data is presented in the following tables.

- T. Demographics (FAS)

- T. Baseline Characteristics (FAS)

## 8.2 Medical History, Concurrent Disease and Surgery

The medical history is classified as past medical history or concurrent disease according to section 6.2. Past medical history, concurrent disease and prior surgery are standardized as "System Organ Class (SOC)" and "Preferred Term (PT)" using MedDRA version 20.0 or higher, and for the FAS, the frequency (N) and percentage (%) are summarized by each treatment group. The differences among treatment groups will be compared using the chi-square test or Fisher's exact test.

A summary of the data is presented in the following tables.

- T. Past Medical History by SOC and PT (FAS)
- T. Current Disease by SOC and PT (FAS)
- T. Prior Surgery by SOC and PT (FAS)

## 8.3 Treatment Compliance and Medication Other Than Study Drug

### 8.3.1 Treatment Compliance

Treatment compliance by visit and overall treatment compliance are presented with the descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) and ANOVA or Kruskal-Wallis test is performed to examine the difference among treatment groups. A summary of the treatment compliance is presented for the FAS.

A summary of the data is presented in the following tables.

- T. Treatment Compliance (FAS)

### 8.3.2 Prior and Concomitant Medication

Medications are categorized according to Section 6.3 and standardized as Anatomical Main Group (ATC level 1) and Therapeutic Subgroup (ATC level 2) using WHO Drug Dictionary Enhanced 2017 or higher. For the FAS, prior and concomitant medications are summarized by frequency (N), percentage (%) and number of occurrence by each treatment group, and the differences among treatment groups are compared using the chi-square test or Fisher's exact test.

A summary of the data is presented in the following tables.

- T. Prior Medications by Anatomical Main Group and Therapeutic Subgroup (FAS)
- T. Concomitant Medications by Anatomical Main Group and Therapeutic Subgroup (FAS)

## 8.4 Efficacy Analysis

The efficacy assessment will be performed based on the FAS and the PPS groups. The FAS group result is considered as the main analysis, but the result of the PPS group should also be presented for the sensitivity analysis.

### 8.4.1 Primary Efficacy Analysis

The primary efficacy endpoint is the percentage of subjects with gallstone formation within 12 months of gastrectomy based on the external investigator's assessment.

For the superiority test of DWJ1319 over placebo on the incidence of gallstone formation, sequential multiple testing will be performed for each treatment group according to the fixed sequence method.

- Step 1: Superiority testing for DWJ1319 600 mg compared with placebo (5% significance level)

- Step 2: Superiority testing for DWJ1319 300 mg compared with placebo (5% significance level)

As DWJ1319 600 mg is expected to be relatively more effective in preventing gallstones compared to DWJ1319 300 mg, the efficacy assessment of DWJ1319 600 mg versus placebo is given priority.

The step 2 test can be performed only if the result of the step 1 test is statistically significant, and conclusions about the superiority of DWJ1319 over placebo will be drawn based on the test result from each step. If the result of the step 1 test is not statistically significant, the step 2 test will not be performed, and it will be concluded that both treatment groups of DWJ1319 have failed to demonstrate superiority over placebo.

The frequency, percentage (%), and corresponding 95% confidence intervals are presented for the subjects with gallstone formation within 12 months by each treatment group. The comparison between each treatment group of DWJ1319 versus the placebo is analyzed using the Logistic Regression Model, with the lymph node resection range (D1+, D2) and the type of gastrectomy (Total gastrectomy, partial gastrectomy) as the covariates and the respective factors are defined as the following. The factors are defined as treatment group (DWJ1319 600 mg vs Placebo) for Step 1, treatment group (DWJ1319 300 mg vs Placebo) for Step 2, and treatment group (Placebo, DWJ1319 600 mg and DWJ1319 300 mg) for sensitivity analysis. Logistic Regression Model results are presented as odds ratios, corresponding 95% confidence intervals and two-sided p-values, and p-value is used for the final determination.

A summary of the data is presented in the following tables.

- T. Percentage of Subjects with Gallstone Formation within 12 month by the External Investigator's Assessment [DWJ1319 600mg vs Placebo] (FAS)

- T. Percentage of Subjects with Gallstone Formation within 12 month by the External Investigator's Assessment [DWJ1319 300mg vs Placebo] (FAS)

- T. Percentage of Subjects with Gallstone Formation within 12 month by the External Investigator's Assessment (FAS)

- T. Percentage of Subjects with Gallstone Formation within 12 month by the External Investigator's Assessment [DWJ1319 600mg vs Placebo] (PPS)

- T. Percentage of Subjects with Gallstone Formation within 12 month by the External Investigator's Assessment [DWJ1319 300mg vs Placebo] (PPS)

- T. Percentage of Subjects with Gallstone Formation within 12 month by the External Investigator's Assessment (PPS)

### 8.4.2 Secondary Efficacy Analysis

1) Percentage of subjects forming gallstones within 3, 6, 9, and 12 months from

gastrectomy

2) Percentage of subjects forming gallstones within 3, 6, and 9 months from gastrectomy as assessed by the external investigator

3) Percentage of subjects forming biliary sludge within 3, 6, 9, and 12 months from gastrectomy

For the secondary endpoints 1), 2), and 3), the comparison between each treatment group of DWJ1319 versus the placebo is analyzed using the Logistic Regression Model, with the treatment groups (DWJ1319 600 mg/DWJ1319 300 mg vs Placebo) as the factor and the lymph node resection range (D1+, D2) and the type of gastrectomy (Total gastrectomy, partial gastrectomy) as the covariates. Logistic Regression Model results are presented as odds ratios, corresponding 95% confidence intervals and two-sided p-values.

4) Time to gallstone formation

For the time to gallstone formation, the median and corresponding 95% confidence intervals, and standard error values are presented. The comparison between each treatment group of DWJ1319 versus the placebo is analyzed using the Cox Proportional Hazards regression Model and the two-sided p-values are presented, with the treatment groups (DWJ1319 600 mg/DWJ1319 300 mg vs Placebo) as the factor and the lymph node resection range (D1+, D2) and the type of gastrectomy (Total gastrectomy, partial gastrectomy) as the covariates.

A summary of the data is presented in the following tables.

- T. Percentage of Subjects with Gallstone Formation within 3, 6, 9, 12 month by the Investigator's Assessment (FAS)

- T. Percentage of Subjects with Gallstone Formation within 3, 6, 9, 12 month by the Investigator's Assessment (PPS)

- T. Percentage of Subjects with Gallstone Formation within 3, 6, 9 month by the External Investigator's Assessment (FAS)

- T. Percentage of Subjects with Gallstone Formation within 3, 6, 9month by the External Investigator's Assessment (PPS)

- T. Percentage of Subjects with Biliary Sludge Formation within 3, 6, 9, 12 month by the Investigator's Assessment (FAS)

- T. Percentage of Subjects with Biliary Sludge Formation within 3, 6, 9, 12 month by the Investigator's Assessment (PPS)

- T. Time to Gallstone Formation (FAS)

- T. Time to Gallstone Formation (PPS)

### 8.4.3 Exploratory Endpoints

1) Change in the biliary reflux symptoms from baseline at 3, 6, 9, and 12 months

For scores of questionnaire on bile reflux symptoms, the score of each typical symptom (upper abdominal pain, heartburn, nausea/sickness) and the total score of symptoms will be presented in three categories which are frequency, intensity, and the level of distress.

*The descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) of the baseline, at 3, 6, 9, and 12 months and variations from the baseline at 3, 6, 9, and 12 months for each treatment group are presented.* The comparison between each treatment group of DWJ1319 versus the placebo is analyzed using the Analysis Of Covariance (ANCOVA) model, with the treatment groups (DWJ1319 600 mg/DWJ1319 300 mg vs Placebo) as the factor and the lymph node resection range (D1+, D2) and the type of gastrectomy (Total gastrectomy, partial gastrectomy) as the covariates. For the ANCOVA model results, present two-sided p-values for least-square mean (LSM), standard error (SE), and the corresponding 95% confidence interval of LSM difference of each treatment group (each treatment group of DWJ1319 - Placebo).

2) Percentage of subjects who experienced biliary reflux according to the upper gastrointestinal endoscopy at 3 and 12 months
3) Percentage of subjects who showed significantly abnormal AST and ALT values at 6 and 12 months

For the exploratory endpoints 2) and 3), the comparison between each treatment group of DWJ1319 versus the placebo is analyzed using the Logistic Regression Model, with the treatment groups (DWJ1319 600 mg/DWJ1319 300 mg vs Placebo) as the factor and the lymph node resection range (D1+, D2) and the type of gastrectomy (Total gastrectomy, partial gastrectomy) as the covariates. Logistic Regression Model results are presented as odds ratios, corresponding 95% confidence intervals and two-sided p-values.

A summary of the data is presented in the following tables.

- T. Change from Baseline in Biliary Reflux Symptom at 3, 6, 9, 12 month by Domain [Parameter: Symptom] (FAS)
- T. Change from Baseline in Biliary Reflux Symptom at 3, 6, 9, 12 month *by Domain* [*Parameter:* Symptom] (PPS)
- T. Change from Baseline in Biliary Reflux Symptom at 3, 6, 9, 12 month by Domain [Parameter: Domain] (FAS)
- T. Change from Baseline in Biliary Reflux *Symptom* at 3, 6, 9, 12 month *by Domain* [*Parameter: Domain*] (PPS)
- T. Change from Baseline in Biliary Reflux Symptom at 3, 6, 9, 12 month [Parameter: Total Score] (FAS)
- T. Change from Baseline in Biliary Reflux *Symptom* at 3, 6, 9, 12 month [*Parameter: Total Score*] (PPS)
- T. Percentage of Subjects with Biliary Reflux at 3, 12 month by Endoscopy (FAS)
- T. Percentage of Subjects with Biliary Reflux at 3, 12 month by Endoscopy (PPS)
- T. Percentage of Subjects with Clinically Significant result for AST at 6, 12 month (FAS)
- T. Percentage of Subjects with Clinically Significant result for AST at 6, 12 month (PPS)
- T. Percentage of Subjects with Clinically Significant result for ALT at 6, 12 month (FAS)
- T. Percentage of Subjects with Clinically Significant result for ALT at 6, 12 month (PPS)

# 9. SAFETY EVALUATION

All safety assessment analysis is conducted on safety set.

## 9.1 Extent of Exposure

In terms of extent of exposure to the investigational product, for the Safety Set, the total dose (㎎), exposure period (days) and average daily dose (㎎/day) are presented with descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) for each treatment group.

A summary of the data is presented in the following tables.

- T. Extent to Exposure (Safety Set)

## 9.2 Adverse Events

Summary and analysis are performed for the Safety Set in cases where adverse events occurred after the administration of the investigational product or the severity of the preceding adverse events worsened (TEAEs: Treatment-Emergent Adverse Events) after the first dose of the investigational product.

All adverse events are standardized as “System Organ Class (SOC)” and “Preferred Term (PT)” using MedDRA version 20.0 or higher.

### 9.2.1 Overall Summary of Adverse Events

The number of subjects, expression rate (%) and the number occurrences of TEAEs and ADRs during the clinical study are presented as well as the 95% confidence intervals for the expression rate. However, a 95% accurate confidence interval for expression rate is presented when a cell with an expected frequency of less than 5 is equal to 20% or higher of all cells. The chi-square test or Fisher's exact test is used to determine whether there is a significant difference among the treatment groups, and the severity of the collected adverse events and their relevance to the investigational product are presented.

Also, serious adverse events, adverse events that resulted in permanent discontinuation of investigational product treatment, and adverse events that resulted in death are summarized.

A summary of the data is presented in the following tables.

- T. Overall Summary of TEAEs (Safety Set)
- T. Overall Summary of ADRs (Safety Set)

### 9.2.2 Display of Adverse Events

The number of subjects, expression rate (%) and the number of cases of all AEs and ADRs during the clinical study are presented according to SOC or PT. Also, the number of subjects, the expression rate (%) and the number of cases are presented for the severity (Mild/Moderate/Severe) according to SOC or PT.

If the same adverse events, based on “PT”, occur multiple times in the same subject, treat it as one occurrence. If the severity and causal relationship are different, treat it with the maximum

causal relationship and severity.

A summary of the data is presented in the following table and list.

- T. Incidence of Most Frequently Occurred(≥n%) TEAEs by SOC and PT (Safety Set)
- T. Incidence of Most Frequently Occurred(≥n%) ADRs by SOC and PT (Safety Set)
- T. Incidence of TEAEs by SOC and PT (Safety Set)
- T. Incidence of ADRs by SOC and PT (Safety Set)
- T. Incidence of TEAEs by Maximum Severity, SOC and PT: DWJ1319 600 mg (Safety Set)
- T. Incidence of TEAEs by Maximum Severity, SOC and PT: DWJ1319 300 mg (Safety Set)
- T. Incidence of TEAEs by Maximum Severity, SOC and PT: Placebo (Safety Set)
- T. Number of TEAEs by Severity, SOC and PT: DWJ1319 600 mg (Safety Set)
- T. Number of TEAEs by Severity, SOC and PT: DWJ1319 300 mg (Safety Set)
- T. Number of TEAEs by Severity, SOC and PT: Placebo (Safety Set)
- T. Incidence of ADRs by Maximum Severity, SOC and PT: DWJ1319 600 mg (Safety Set)
- T. Incidence of ADRs by Maximum Severity, SOC and PT: DWJ1319 300 mg (Safety Set)
- T. Incidence of ADRs by Maximum Severity, SOC and PT: Placebo (Safety Set)
- T. Number of ADRs by Severity, SOC and PT: DWJ1319 600 mg (Safety Set)
- T. Number of ADRs by Severity, SOC and PT: DWJ1319 300 mg (Safety Set)
- T. Number of ADRs by Severity, SOC and PT: Placebo (Safety Set)
- L. Subjects with TEAEs (Safety Set)
- L. Subjects with Pre-Treatment AEs (Safety Set)

#### 9.2.3 Death and Serious Adverse Events and Other Significant Adverse Events

For the serious adverse events, adverse events that resulted in permanent discontinuation of investigational product administration, and adverse events that resulted in death, based on SOC or PT, the number of subjects, expression rate (%) and the number of cases are presented for each treatment group.

A summary of the data is presented in the following tables and lists.

- T. Incidence of Serious TEAEs by SOC and PT (Safety Set)
- T. Incidence of Serious ADRs by SOC and PT (Safety Set)
- T. Incidence of TEAEs Leading to IP Discontinuation by SOC and PT (Safety Set)
- T. Incidence of ADRs Leading to IP Discontinuation by SOC and PT (Safety Set)
- T. Incidence of TEAEs Leading to Death by SOC and PT (Safety Set)
- T. Incidence of ADRs Leading to Death by SOC and PT (Safety Set)
- L. Subjects with Serious TEAEs (Safety Set)

- L. Subjects with TEAEs Leading To IP Discontinuation (Safety Set)
- L. Subjects with TEAEs Leading To Death (Safety Set)

#### 9.2.4 Evaluation of Each Laboratory Parameter

For the continuous variables of the clinical laboratory test categories, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) are presented for each treatment group with respect to the measured value and the change relative to the baseline at each visit. For intra-group changes relative to the baseline, paired t-test or Wilcoxon signed rank test is performed for comparison according to the result of the normality test. For the differences among the treatment groups, ANOVA or Kruskal-Wallis test is performed for comparison according to the result of the normality test.

A summary of the data is presented in the following tables.

- T. Summary of Hematology Data [Parameter] (Safety Set)
- T. Summary of Serum Chemistry Data [Parameter] (Safety Set)
- T. Summary of Urinalysis Data [Parameter] (Safety Set)

In order to confirm any changes in normality status after the administration of the investigational product compared to the baseline, data is divided into the normal, abnormal NCS and abnormal CS categories and summarized in shift table form by treatment group at each evaluation point. The McNemar's test is used for intra-group changes and the chi-square test or the Fisher's exact test is used to compare differences among the treatment groups. In addition, a list is presented of subjects who were normal or abnormal NCS at baseline but showed abnormal CS changes after administration of the investigational product.

A summary of the data is presented in the following table and list.

- T. Shift from Baseline at Post-Baseline on Hematology Data [Parameter] (Safety Set)
- T. Shift from Baseline at Post-Baseline on Serum Chemistry Data [Parameter] (Safety Set)
- T. Shift from Baseline at Post-Baseline on Urinalysis Data [Parameter] (Safety Set)
- L. Subjects Shifting from Normal or NCS at Baseline to CS at Post-Treatment on Laboratory (Safety Set)

### 9.3 Other Safety Measures

#### 9.3.1 Vital Signs

For the vital signs, descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum values) are presented for each treatment group with respect to the measured value and the change relative to the baseline at each visit. For intra-group changes relative to the baseline, paired t-test or Wilcoxon signed rank test is performed for comparison according to the result of the normality test. For the differences among the treatment groups, ANOVA or Kruskal-Wallis test is performed for comparison according to the result of the normality test.

A summary of the data is presented in the following table.

- T. Summary of Vital Signs [Parameter] (Safety Set)

### 9.3.2 Physical Examination

For physical examination results at each visit, the number of subjects and percentage (%) are presented for normal, abnormal NCS, and abnormal CS categories, and a list is presented for subjects who were indicated as abnormal CS. If the same adverse events, based on “PT”, occur multiple times in the same subject, treat it as one occurrence. If the severity and causal relationship are different, treat it with the maximum causal relationship and severity.

A summary of the data is presented in the following table and list.

- T. Physical Examination (Safety Set)
- L. Subjects with Abnormal CS on Physical Examination (Safety Set)

# 10. ADDITIONAL EVALUATION

NA

# 11. GENERAL PRESENTATION OF SUMMARIES AND ANALYSES

## 11.1 Significance Level

Unless otherwise specified, all tests are set at a significance level of 0.05 and are subject to testing on two-sided tests in principle.

## 11.2 Summary Statistics

Unless otherwise specified, the number of subjects, mean, standard deviation, median, minimum, and maximum values are presented for continuous variables, and frequency and percentage (%) are presented for categorical data.

## 11.3 Decimals

When descriptive statistics such as number of subjects, mean, standard deviation, median, minimum, and maximum values are presented in percentage (%) for the continuous variables, it is presented up to two decimal places. For p-value, it is displayed up to four decimal places. If the calculated p-value is less than 0.0001, it is presented as '<0.0001'.

Summaries of vital signs and clinical laboratory tests are rounded to the number of significant digits, that is, the maximum number of digits below the decimal point for each item.

## 11.1 Statistical Analysis Methods

When a confidence interval for a ratio is presented, an accurate confidence interval is presented when a cell with an expected frequency of less than 5 is equal to 20% or higher of all cells. In addition, if the odds ratio is estimated to be infinite including the cell with a frequency of 0 when presenting the odds ratio, the odds ratio is estimated using Firth's Penalized Maximum Likelihood and a profile-likelihood confidence interval is presented.

## 11.2 Baseline

Unless otherwise specified, the baseline is defined as the last measurement prior to the dose of investigational product without missing data.

## 11.3 Study Period and Visit Window Definitions

Unless otherwise specified, the point-by-point summary of each assessment variable is presented for the regular visit measurement.

| Visit | Analysis Label | Actual Point | Visit Window |
|---|---|---|---|
| Visit 1 | Screening | - 2 week~ - Day1 | |
| Visit 2 | Baseline | Day 1 | |
| Visit 3 | 3 month | 3 month | ± 1 week |
| Visit 4 | 6 month | 6 month | ± 1 week |
| Visit 5 | 9 month | 9 month | ± 1 week |
| Visit 6 | 12 month | 12 month | ± 1 week |

### 11.4 Software for Statistical Analysis

All statistical analysis will be performed using SAS® Version 9.4 or higher (SAS institute, Cary, NC, USA).

## 12. DATA HANDLING COVENTIONS

### 12.1 Handling of Missing Data

#### 12.1.1 Missing Value of Efficacy Variables

If there is a missing value due to the withdrawal of the subject before the end of the clinical study or a missing a test at a particular point in time, unless otherwise specified, the data is not replaced for analysis but treated as an observed case.

#### 12.1.2 Missing Value of Safety Variables

If there is missing data in analyzing the Safety Set, the analysis is carried out as is without replacing it.

### 12.2 Repeated or Unscheduled Assessments

For all endpoints, if there is more than one measurement result prior to the first dose of the investigational product, use the baseline value as defined in Section 11.4.

If there is a measurement result on an unscheduled visit after the first dose of the investigational product, on the list of the subject, present it sequentially with the regular visits based on the visit date.

A summary of measurements by time point is presented only for regular visits and not presented separately for unscheduled visits. However, the final result excluding the baseline of the subject that was withdrawn are summarized together with the results of the last visit of the regular visit. In addition, only the results of regular visits are used to test for statistical significance.

### 12.3 Handling of Incomplete Date

If part of the day or month data is missing from the start or end date of the medical history and

prior surgery, concomitant mediation, and adverse events, comparison is made based on the collected data without replacing the dates. However, if all start dates are missing, regard it as starting prior to the first dose of investigational product, and if the end date is missing, regard it as currently being administered.

### 12.4 Character Values of Clinical Laboratory Evaluation

If any of the measurements of the clinical laboratory results are collected including a sign of inequality, replace it as the following to summarize. When presenting a list by subject, present the recorded values in the CRF.

- If recorded as equal or above (i.e., >=100 or >100), replace with minimum value (i.e., 100)
- If recorded as equal or below (i.e., <=4 or <4), replace with maximum value (i.e., 4)

## 13. INTERIM ANALYSIS

An interim analysis was not planned in this study.

## 14. CHANGE FROM PROTOCOL

| Categor | Protocol | Statistical Analysis Plan | Reasons for Change |
|---|---|---|---|
| Determination of gallstones | The diagnosis of gallstone formation is based primarily on the results of abdominal ultrasound and is supplemented by abdominal CT scan results. If the results of the two tests differ, abdominal ultrasound result should be considered first for gallbladder gallstones, and both abdominal ultrasound and abdominal CT should be considered in the case of bile duct gallstones or intrahepatic bile duct gallstones. | The diagnosis of gallstone formation is based primarily on the results of abdominal ultrasound and is supplemented by abdominal CT scan results. If the results of the two tests differ, abdominal ultrasound result should be considered first for gallbladder gallstones, and both abdominal ultrasound and abdominal CT should be considered in the case of bile duct gallstones or intrahepatic bile duct gallstones. <u>If only the abdominal CT scan result is available, utilize the available CT scan result for the diagnosis of gallstone formation.</u> | Additional techniques for cases in which only abdominal CT scan results are available. |

# 15. SAS PROCEDURE FOR TESTING

## 15.1 Normality Test

```
PROC UNIVARIATE DATA=dataset NORMAL;
  VAR variable;
RUN;
```

## 15.2 Testing for Within-Groups

**Paired t-test or Wilcoxon signed-rank test**

```
PROC UNIVARIATE DATA=dataset;
  VAR diff;
RUN;
```

**McNemar's Test**

```
PROC FREQ DATA=dataset;
  TABLE treatment* variable/AGREE;
RUN;
```

## 15.3 Comparison for Between Treatment Groups

**ANOVA**

```
PROC GLM DATA = dataset;
  CLASS treatment;
  MODEL variable = treatment;
RUN;
```

**Kruskal-Waillis test**

```
PROC NPAR1WAY DATA = dataset WILCOXON;
  CLASS treatment;
  VAR variable;
RUN;
```

**Chi-square or Fisher's exact test**

```
PROC FREQ DATA = dataset;
  TABLE treatment * variable/CHISQ FISHER;
RUN;
```

**ANCOVA**

```
PROC GLM DATA = dataset;
  CLASS treatment covariate (categorical);
  MODEL variable = treatment covariate;
  LSMEANS treatment/PDIFF CL STDERR;
  ESTIMATE 'DWJ1319 600 mg or 300 mg vs Placebo' treatment 1 -1;
RUN;
```

**Logistic regression model**

```
PROC LOGISTIC DATA = dataset;
  CLASS treatment covariate (categorical)/param=ref ref=last;
  MODEL variable = treatment covariate;
```

```
   ESTIMATE 'DWJ1319 600 mg or 300 mg vs Placebo' treatment 1 -1 /EXP;
RUN;

Logistic regression model (in case of including cells with frequency of 0)
PROC LOGISTIC DATA = dataset;
   CLASS treatment covariate (categorical)/param=ref ref=last;
   MODEL variable = treatment covariate/ firth clodds=pl;
RUN;


Cox Proportional Hazards regression Model
PROC PHREG DATA = dataset;
   CLASS treatment covariate (categorical)/param=ref ref=last;
   MODEL time * status(censored) = treatment covariate / RL;
   CONTRAST 'DWJ1319 600 mg or 300 mg vs Placebo' treatment 1 -1 / ESTIMATE =EXP;
RUN;
```

## 16. REFERENCES

SAS/STAT® 14.3 User's Guide The LOGISTIC Procedure, 2017, SAS Institute Inc., Cary, NC, USA

## Appendix. LIST OF TABLES, FIGURES AND LISTINGS

***1. Mock-Up Tables***

***2. Mock-Up Figures***

***3. Mock-Up Listings***