ABSTRACT

Introduction: SO-1105 is an oral mucosal adhesive tablet containing 50 mg of miconazole. It had been shown overseas that a once-daily application of the drug continues antifungal effect in the treatment of oropharyngeal candidiasis. We report the results of the phase 3 clinical study of this drug with miconazole gel as a control in Japan. Methods: The study included patients aged 20 years or older with oropharyngeal candidiasis who had oral lesions characterized by oropharyngeal candidiasis and whose fungi was confirmed by direct microscopic examination. The primary efficacy endpoint was the clinical cure rate on Day 15 after 14 days of administration. The population analyzed for efficacy was per protocol set (PPS). Results: 120 subjects were included in PPS. In detail, 59 subjects were in the SO-1105 group (SO-1105 group) and 61 subjects were in the miconazole gel group (Gel group). For efficacy, the clinical cure rate on Day 15 was 47.5% in SO-1105 group and 47.5% in Gel group, showing the similar efficacy between both groups. For safety, adverse drug reactions were observed in 29.0% of SO-1105 group and 24.6% of Gel group, showing the similar safety between both groups. Conclusion: The efficacy of SO-1105 was shown to be similar to that of miconazole gel. Meanwhile, SO-1105 is an adhesive tablet and is administered once-daily. For this, SO-1105 is expected to better compliance and useful drug for the elderly. Therefore, SO-1105 is considered to be widely used in clinical practice as one of the therapeutic drugs for oropharyngeal candidiasis.

Key words: adherence tablets, candidiasis, drug adherence, miconazole, SO-1105
Introduction

Oropharyngeal candidiasis (OPC) is an oral mucosal inflammatory disease caused by candida belonging to fungus. OPC can be clinically classified into acute and chronic types. Pathologically, the acute type can be subdivided into pseudomembranous and atrophic/erythematous subtypes, and the chronic type can be subdivided into hyperplastic and atrophic/erythematous subtypes.

1. Existing therapeutic drugs for oropharyngeal candidiasis

The treatment for OPC includes topical and systemic therapies with antifungals. Topical antifungal drugs are recommended as one of first-line drugs by the Infectious Diseases Society of America1. Examples of topical therapies include miconazole oral gel, amphotericin B syrup and clotrimazole troche indicated only for oral candidiasis in patients with Human Immunodeficiency Virus (HIV) infection. However, these formulations involve problems of frequent daily dosing (4-5 doses/day) to obtain sufficient therapeutic effects by extending the oral retention time of the active ingredient, and drug resistance2.

Systemic therapeutic drugs include fluconazole capsules and itraconazole tablet, capsule and oral solution. These systemic therapies provide sufficient effects when administered once daily and have no problems in dosing frequency. However, these drugs may cause adverse drug reactions due to systemic circulation and may increase their blood concentrations by inhibiting the metabolism of other drugs due to inhibition of hepatic cytochrome P450.

2. Miconazole

Miconazole is a synthetic imidazole antifungal with broad spectrum and shows wide activity on Candida species. Currently, various formulations of miconazole have been developed inside and outside of Japan to address a variety of mycoses and have been widely used in clinical practice for 30 years or longer. Topical formulations of miconazole nitrate have been designated as essential medicines by the World Health Organization (WHO). The efficacy, safety and pharmacokinetic profiles of various miconazole formulations have been clarified in a number of domestic and overseas studies3.

In the formulations, miconazole oral gel has a problem of discomfort in use4, and it is hard to say that it is a fully satisfactory treatment from the viewpoint of medication adherence and Quality of Life (QOL) of patients. Additionally, it is concerned that therapeutic effect may decrease due to decrease in medication adherence, and it has been pointed out that this may easily lead to a situation where sufficient drug efficacy cannot be obtained or the disease repeatedly relapses5.

3. Features of SO-1105

SO-1105 (product name: ORAVI® mucoadhesive tablets 50 mg) is an oral mucoadhesive tablet containing 50 mg of miconazole (base) in one tablet. SO-1105 is administered once daily and is designed so that miconazole can be released continuously into the oral cavity by persistent adherence to oral mucosa. It has been confirmed to show a prolonged antifungal action for treatment of OPC6.

SO-1105 is already on the market in 3 countries, i.e., France, Italy and the United States.

We conducted a phase III clinical study in Japan from 2013 to 2016, with Sosei Co., Ltd. as the sponsor. The purpose of the study was to compare the clinical efficacy and safety of SO-1105 and miconazole gel in patients with oropharyngeal candidiasis, and hereby report the results.

Methods

1. Patients

The subjects were patients with OPC aged 20 years or older, who met all of the inclusion criteria shown in Table 1 such as oral lesions (e.g. white moss, erythema) and direct microscopic confirmation of fungi and none of the exclusion criteria shown in Table 2. The target sample size was 120 subjects in total for both groups, in which 20 or more of them were patients with head and neck cancer after radiation therapy as a pathogenesis of OPC. The study was conducted at 20 clinical sites in Japan.

2. Informed consent

The details of the study and other matters related to the study were appropriately explained to the subjects using the informed consent form and other documents in accordance with the Good Clinical Practice Ministerial Ordinance (J-GCP) before they could participate in this study, and written informed consent was obtained from all subjects based on their own free will.

3. Study drugs

SO-1105 and miconazole gel containing 100 mg of miconazole in 5 g tubes (brand name: FLORID Oral gel 2%, Mochida Pharmaceutical Co., Ltd.) were used as the investigational drug and the control drug respectively.

4. Study method

The study was designed as a multicenter, open-label, randomized, active-controlled, parallel-group comparison. The eligible subjects were randomized to receive SO-1105 (50 mg/day as miconazole) or miconazole gel (400 mg/day as
miconazole) by dynamic allocation with pathogenesis as stratification factor of “post-radiation therapy for head and neck cancer”, “immune disorders”, “drug-induced disorder” and “others”. One tablet of SO-1105 was adhered to the maxillary gingiva (canine fossa) once daily following brushing of the teeth after breakfast (Fig. 1), and one tube of miconazole gel per dose was applied and kept as long as possible (2-3 minutes) in the mouth four times daily, i.e., after each meal and before bedtime, and then swallowed. Both drugs were administered daily for 14 consecutive days. The study period was defined to include screening period of 9 days before the start of treatment, administration period of 14 days, and follow-up period of 29 days from the treatment completion (Fig. 2). The amount of saliva as one of subject characteristics was classified into “absent”, “partial”, or “normal”.

### 5. Endpoints

The primary endpoint was the cure rate on Day 15, and the key secondary endpoints were lesion improvement rate (the rate of patients in whom candidiasis lesions improved) on Day 15, symptom improvement rate (the rate of patients in whom candidiasis symptoms improved) on Day 15, clinical cure rate (the rate of patients in whom candidiasis resolved) on Day 8, success rate (the proportions of patients in whom candidiasis disappeared and in whom it improved) on Day 8 and 15, relapse rate (the rate of patients in whom candidiasis relapsed) on Day 29 and negative fungal culture rate (the rate of patients in whom the fungus was negative) on Day 15 (Table 3).

For clinical efficacy, oral lesions and symptoms (soreness/burning) of OPC were scored according to the assessment

---

**Table 1. Inclusion criteria**

| Inclusion criteria |  |
|--------------------|---|
| Patients who met all of the following 5 criteria were eligible. |  |
| 1. Age 20 or older at informed consent |  |
| 2. Oral lesions with the clinical features of oropharyngeal candidiasis (e.g., white moss, erythema) |  |
| 3. Fungal detection by direct microscopy |  |
| 4. No risk of a marked deterioration in general health occurring between the informed consent and the end of the study |  |
| 5. Able to provide voluntary, written consent to participate in the study |  |

**Table 2. Exclusion criteria**

| Exclusion criteria |  |
|--------------------|---|
| Patients who met any of the following 14 criteria were ineligible. |  |
| 1. Unable to take the study drug due to the use of dentures, etc., as judged by the investigator or sub-investigator |  |
| 2. ECOG grade ≥ 3 |  |
| 3. Received systemic antifungals within 2 weeks before the start of study treatment |  |
| 4. Received local antifungals within 1 week before the start of study treatment |  |
| 5. Used prohibited concomitant medications within 2 weeks before the start of study treatment or expected to use such medications during the study period |  |
| 6. Had undergone radiation therapy for head and neck cancer within 4 weeks before the start of study treatment or expected to receive such therapy during the study period |  |
| 7. Prior or concurrent hypersensitivity to Imidazole derivatives |  |
| 8. Prior or concurrent milk allergy or hypersensitivity to one of the components of the study drug |  |
| 9. Hereditary galactose intolerance, lactase enzyme deficiency, or glucose/ galactose malabsorption |  |
| 10. ALT or AST > 3 times the upper limit of normal (ULN) of the central laboratory, or prior or concurrent serious liver disease |  |
| 11. Pregnant women, women who may be pregnant, women who wish to become pregnant during the study period, or lactating women |  |
| 12. Unable to comply with the protocol-defined procedures, as judged by the investigator or sub-investigator |  |
| 13. Participated in other clinical studies or post-marketing clinical studies within 4 months before informed consent |  |
| 14. Inappropriate to evaluate the efficacy and safety of the study drug for other reasons as judged by the investigator or the sub-investigator |  |

---

Fig. 1. How to take the tablet (SO-1105).
(a) Position the tablet, with the flat surface facing the cheek mucosa, by using fingers and apply it to the gum in the right or left canine fossa.
(b) Keep fingers on the outside of upper lip and hold the tablet in place for 30 seconds to facilitate adhesion to the gum.

Fig. 2. Study schedule.
Table 3. Efficacy assessments

Primary endpoint
- Clinical cure rate (the rate of patients in whom candidiasis resolved) on Day 15

Secondary endpoints
- Lesion improvement rate (the rate of patients in whom candidiasis lesions improved) on Day 15
- Symptom improvement rate (the rate of patients in whom candidiasis symptoms improved) on Day 15
- Clinical cure rate (the rate of patients in whom candidiasis resolved) on Day 8
- Success rates (the proportions of patients in whom candidiasis disappeared and in whom it improved) on Days 8 and 15
- Relapse rate (the rate of patients in whom candidiasis relapsed) on Day 29
- Negative fungal culture rate (the rate of patients in whom the fungus was negative) on Day 15

Table 4. Assessment criteria for oral lesions score and symptoms score

| lesions score | symptoms score (soreness/burning) |
|---------------|----------------------------------|
| 0: none       | 0: absent                        |
| 1: single, localized | 1: mild                        |
| 2: multiple, localized | 2: moderate                    |
| 3: extensive or confluent | 3: severe                    |

Table 5. Evaluation for clinical efficacy

| Oral lesions score | Symptoms (soreness/burning) score | Assessment       |
|--------------------|----------------------------------|------------------|
| Score 0            | Score 0                          | Clinical Cure    |
| Score 0            | Score 1 *                        | Clinical Improvement |
| No change–decrease of 1 score or greater | No change–decrease of 1 score or greater | Partial Improvement ** |
| No change          | No change                        | No change        |
| Increase of 1 score or greater | Increase of 1 score or greater | Deterioration *** |

* Excluding cases with pre- and post-dose scores of “1” to “1."
** Excluding cases where the lesions score at the time of evaluation is “no change” and the symptoms score is “no change.”
*** At least one of the lesions score or symptoms score at the time of evaluation has increased 1 score or more.

Table 6. Analysis method

In this study, the number of subjects who achieved Clinical cure on Day 15 as the primary endpoint, the cure rate and its 95% confidence interval were calculated for each treatment group and compared between them. With pathogenesis of OPC as stratification factors, the number of subjects who achieved Clinical cure on Day 15, the cure rate and its 95% confidence interval were calculated for each stratum and compared between the two treatment groups.

Efficacy analysis population was the Per Protocol Set (PPS), and the same analysis was conducted on the Full Analysis Set (FAS) for reference. Safety analysis population was FAS. The FAS is a population of subjects who took any study drugs at least once after enrollment in the study. The PPS is a population after excluding subjects with protocol deviations from the FAS that may affect efficacy evaluation. Fisher’s exact test, Wilcoxon rank sum test, or Student’s t-test was used as statistical test (SAS SYSTEM Ver. 9.2, SAS Institute Japan Ltd.). Significance level was set at two-sided 5%. When comparability of background factors was examined, two-sided 15% was used as a rough standard. The test was used just as an aim for interpretation of the results, and the p value was represented as a numerical value.

Results

1. Disposition of subjects

The study drugs were assigned to a total of 124 randomized subjects. Of these, 123 subjects who received at least one dose of the study drugs, of which 62 subjects were in the SO-1105
group (SO-1105 group) and 61 subjects were in the miconazole gel group (Gel group), constituted the FAS. In the FAS, 120 subjects (59 subjects in SO-1105 group, 61 subjects in Gel group) except for 3 subjects in SO-1105 group who had significant deviations from the protocol (compliance deviation and withdrawal during treatment period), constituted the PPS (Fig. 3).

2. Subject characteristics
Baseline characteristics of subjects who complied with the protocol as the PPS were examined (Table 6). Male and female accounted for 42.4% (25/59) and 57.6% (34/59) respectively in SO-1105 group, and for 36.1% (22/61) and 63.9% (39/61) respectively in Gel group. The mean ± SD for age was 66.3 ± 11.2 years old in SO-1105 group and 68.4 ± 12.6 years old in Gel group. There were no notable differences in these background factors between the two treatment groups.

The disposition of pathogenesis as the stratification factors was similar in the order of category as follows: “others” for 47.5% (28/59), “drug-induced disorder” for 23.7% (14/59), “post-radiation therapy for head and neck cancer” for 22.0% (13/59) and “immune disorders” for 6.8% (4/59) in SO-1105 group, and “others” for 49.2% (30/61), “drug-induced disorder” for 23.0% (14/61), “post-radiation therapy for head and neck cancer” for 19.7% (12/61) and “immune disorders” for 8.2% (5/61) in Gel group. There were also no notable differences between the two treatment groups in the amount of saliva and the symptom score. On the other hand, a statistical bias was observed in the pathology of OPC and the lesion score (Fisher’s exact test: p = 0.0359 and Wilcoxon rank-sum test: p = 0.0718). Concerning the pathology of OPC, while “atrophic/erythematous” and “pseudomembranous + atrophic/erythematous (P + A/E)” which were relatively biased, accounted for 17.0% (10/59) and 18.6% (11/59) respectively in SO-1105 group, in which the number of subjects was comparable among the factors, and the both accounted for 36.1% (22/61) and 6.6% (4/61) respectively in Gel group, in which more subjects had “atrophic/erythematous” lesions. Concerning the lesion score, “single, localized,” “multiple, localized” and “extensive or confluent” accounted for 15.3% (9/59), 33.9% (20/59) and 50.9% (30/59) in SO-1105 group respectively, and 23.0% (14/61), 42.6% (26/61) and 34.4% (21/61) in Gel group respectively, showing more subjects with a high lesion score in SO-1105 group.

Candida albicans was most frequently isolated at baseline and accounted for the majority of cases.

3. Efficacy
The cure rate [95% CI] on Day 15 as the primary endpoint was 47.5 [34.3 - 60.9] % (28/59) in SO-1105 group and 47.5 [34.6 - 60.7] % (29/61) in Gel group respectively, which was the same. As a result of clinical efficacy evaluation, while there were no differences in the number of subjects determined as “Clinical cure” (the cure rate) between the two treatment groups, the number of subjects determined as “Partial improvement” or “No change” were 23 subjects (39.0%) and 4 subjects (6.8%) respectively in SO-1105 group, and 19 subjects (31.2%) and 11 subjects (18.0%) respectively in Gel group, showing more subjects determined as “Partial improvement” in SO-1105 group (Fig. 4). The cure rate [95% CI] in the FAS was 46.8 [34.0 - 59.9] % (29/62) in SO-1105 group and 47.5 [34.6 - 60.7] % (29/61) in Gel group respectively, which was comparable between the two groups. Incidentally, 2 subjects with missing data at Day 15 in SO-1105 group were handled as no cure (Fig. 5).

The results of the key secondary endpoints in the PPS are shown in Table 7. The lesion improvement rate on Day 15 evaluated based on the lesion score was slightly higher in SO-1105 group than Gel group, and the negative fungal culture rate was slightly lower in SO-1105 group than Gel group. The results of the other secondary endpoints were comparable between the two treatment groups.

The cure rate for each subgroup on Day 15 according to pathogenesis of OPC (post-radiation therapy for head and neck cancer, immune disorders, drug-induced disorder and others) is shown in Fig. 6. In the comparison among the subgroups of “post-radiation therapy for head and neck cancer”, “immune disorders”, “drug-induced disorder”, and “others”, there was not a large difference in the cure rate between the two treatment groups.

The cure rate on Day 15 according to the amount of saliva was 25.0% (1/4) and 33.3% (1/3) for “absence”, 44.4% (12/27) and 52.8% (19/36) for “partial”, and 53.6% (15/28) and 40.9% (9/40) for “normal” in SO-1105 group and Gel group respectively.
| Subject | SO-1105 group | Gel group | test |
|---------|---------------|-----------|------|
| **Gender** |               |           |      |
| male    | 25 (42.4)     | 22 (36.1) | Fisher’s exact test p = 0.5753 |
| female  | 34 (57.6)     | 39 (63.9) |      |
| **Age (Year)** |       |           | t-test p = 0.3552 |
| mean ± SD | 66.3 ± 11.2  | 68.4 ± 12.6 |      |
| **Causality** |     |           | Fisher’s exact test p = 0.9917 |
| post-radiation therapy for h/n cancer | 13 (22.0) | 12 (19.7) |      |
| immune disorders | 4 (6.8) | 5 (8.2) |      |
| drug-induced disorder | 14 (23.7) | 14 (23.0) |      |
| others | 28 (47.5) | 30 (49.2) |      |
| **OPC** | | | Fisher’s exact test p = 0.0359 |
| pseudomembranous (P) | 32 (54.2) | 31 (50.8) |      |
| atrophic / erythematous (A/ E) | 10 (17.0) | 22 (36.1) |      |
| hyperplastic (H) | 3 (5.1) | 4 (6.6) |      |
| P + A/ E | 11 (18.6) | 4 (6.6) |      |
| P + H | 1 (1.7) | 0 (0.0) |      |
| A/ E + H | 2 (3.4) | 0 (0.0) |      |
| P + A/ E + H | 0 (0.0) | 0 (0.0) |      |
| **Clinical type of candidiasis** | | | Fisher’s exact test p = 0.6957 |
| no | 39 (66.1) | 43 (70.5) |      |
| yes | 20 (33.9) | 18 (29.5) |      |
| **History of antifungal treatment** | | | Wilcoxon rank sum test p = 0.3047 |
| 0 (absence) | 4 (6.8) | 3 (4.9) |      |
| 1 (partial) | 27 (45.8) | 36 (59.0) |      |
| 2 (normal) | 28 (47.5) | 36 (59.0) |      |
| **Saliva production (Day 1)** | | | Wilcoxon rank sum test p = 0.0718 |
| 0 (absence) | 4 (6.8) | 3 (4.9) |      |
| 1 (partial) | 27 (45.8) | 36 (59.0) |      |
| 2 (normal) | 28 (47.5) | 36 (59.0) |      |
| **Lesions score (Day 1)** | | | Wilcoxon rank sum test p = 0.7421 |
| single, localized | 9 (15.3) | 14 (23.0) |      |
| multiple, localized | 20 (33.9) | 26 (42.6) |      |
| extensive or confluent | 30 (50.9) | 21 (34.4) |      |
| **Symptoms score (Day 1)** | | | Fisher’s exact test p = 0.3772 |
| none | 18 (30.5) | 18 (29.5) |      |
| mild | 21 (35.6) | 20 (32.8) |      |
| moderate | 14 (23.7) | 16 (26.2) |      |
| severe | 6 (10.2) | 7 (11.5) |      |
| **Candida species** <sup>*</sup> (Screening period) | | |      |
| C. albicans | 46 (79.3) | 41 (67.2) |      |
| C. glabrata | 0 (0.0) | 4 (6.6) |      |
| C. tropicalis | 1 (1.7) | 3 (4.9) |      |
| C. parapsilosis | 0 (0.0) | 1 (1.6) |      |
| C. krusei | 0 (0.0) | 1 (1.6) |      |
| C. lusitaniae | 0 (0.0) | 1 (1.6) |      |
| C. albicans + C. glabrata | 6 (10.3) | 5 (8.2) |      |
| C. albicans + C. tropicalis | 2 (3.5) | 2 (3.3) |      |
| C. albicans + C. parapsilosis | 1 (1.7) | 1 (1.6) |      |
| C. albicans + C. krusei | 0 (0.0) | 1 (1.6) |      |
| C. albicans + C. kefyr | 0 (0.0) | 1 (1.6) |      |
| C. glabrata + C. tropicalis | 1 (1.7) | 0 (0.0) |      |
| C. albicans + C. glabrata + C. tropicalis | 1 (1.7) | 0 (0.0) |      |

* Excluding one subject of SO-1105 group in which fungal culture was negative.
4. Safety

The incidence of adverse events in the FAS as safety analysis population of 123 subjects was 53.2% (33/62) and 55.7% (34/61) in SO-1105 group and Gel group respectively. The incidence of adverse drug reactions for which a causal relationship with the study drug cannot be denied was 29.0% (18/62) and 24.6% (15/61) in SO-1105 group and Gel group respectively, which was similar in the two treatment groups. In addition, all adverse drug reactions in both groups were mild. The incidence of adverse drug reactions observed in 2 or more subjects who received study drug treatment were dysgeusia occurred in 5 subjects (8.1%), application site discomfort in 3 subjects (4.8%), abdominal discomfort and nausea in 2 subjects (3.2%) in SO-1105 group. Similarly, dysgeusia occurred in 4 subjects (6.6%), and application site irritation in 2 subjects (3.3%) in Gel group. No deaths or serious adverse drug reactions were observed (Table 8).

Discussion

Therapeutic drugs for OPC to be used topically are expected to be advantageous to mitigate systemic adverse drug reactions and drug interactions. Meanwhile, they have disadvantage due to the necessity of frequent administration. In addition, miconazole gel, which is widely used in clinical settings as one of the first-line drugs, has a feeling of use and a bad taste. Therefore, clinicians wanted a therapeutic drug that are more convenient and easier to use.

SO-1105 is a tablet with one curved surface and an opposite flat surface, which has been designed to easily adhere to
maxillary gingiva (canine fossa). In addition, the drug includes milk protein concentrate (MPC) of bioadhesive substance as an excipient adheres to oral mucosa for a long period to continuously release miconazole as the active ingredient in oral cavity over a long time, making it possible to maintain high concentration of miconazole in saliva at the minimum inhibitory concentration or higher required to treat OPC. Since the formulation was designed to have a sustained antifungal effect as described above, once-daily oral mucosal administration of the drug is sufficient\(^6\). This is based on a report regarding comparison of miconazole concentration in saliva between SO-1105 and the miconazole gel with the previous study which showed that SO-1105 maintained high concentrations of miconazole in saliva for long hours and more stably\(^7,8\). and other report that miconazole concentration in saliva after once administration of SO-1105 was 100 µg/mL or higher at 8 hours post dose and sustained for 24 hours postdose\(^9\).

In this study, the efficacy and safety of SO-1105 for OPC without identifying pathogenesis were comparatively investigated with the existing therapeutic drug, miconazole gel. Although the amount of miconazole per day in SO-1105 is low, i.e., 1/8 of the amount in miconazole gel, its clinical efficacy was comparable to that of miconazole gel. Furthermore, concerning the cure rate on Day 15 according to pathogenesis of disease, there were no strata in which the cure rate of SO-1105 was significantly different from that of miconazole gel while there were strata with a small sample size and the accuracy of evaluation was low. These results suggested that SO-1105 is considered to be as effective as the miconazole gel for OPC. Although a bias between the two treatment groups was found in pathology of OPC and the lesion score, which were considered to affect efficacy evaluation, the odds ratio of SO-1105 to the miconazole gel before adjustment was 0.997 and the odds ratio of pathology of OPC and the lesion score (Day 1) adjusted by the Mantel-Haenszel method was 1.008 and 1.051 respectively, for the cure rate on Day 15 as the primary endpoint (PPS), and they are both comparable to the values before adjustment; effects of bias of these covariates are considered to be small for comparison of the cure rates. The lesion improvement rate on Day 15 was slightly higher in SO-1105 group than Gel group, and the negative fungal culture rate was slightly lower in SO-1105 group than Gel group. The reason why both evaluations tended to be different as described above is that negative pathogenic fungus of OPC is considered to be one of rational indices for evaluating effect of drugs, however in the case of antifungals, evaluations tends to vary, for example, as different fungal strains are identified before and after drug treatment due to other causes than drug efficacy such as subject characteristics (e.g., dietary habits and oral hygiene). In this study as well, different trends in both evaluations were considered to be found due to many cases of different strains from the pathogenic fungus isolated after treatment.

The incidence of adverse drug reactions of SO-1105 was comparable to that of the miconazole gel, and there were no problems with the safety profiles.

The drug is the first adhesive tablet for the indication of OPC in Japan. Therefore, some precautions for application should be considered. First, since the main ingredient of MPC which is a bioadhesive substance is milk protein, SO-1105 is contraindicated in patients with a history of milk protein allergy. Incidentally, the amount of MPC contained in one tablet is less than 28 mg and it is equivalent to less than 1 mL in terms of raw milk\(^3\).

Next, the location of adhesion of SO-1105 on oral mucosa is gingiva of left or right-side canine fossa of upper jaw. However, since this location is anatomically unfamiliar to physicians, it may be a problem that it is difficult for them to understand the location and method of adhesion, etc. Furthermore, when SO-1105 is used in patients with lost canine teeth, patients wearing dentures or patients with edentulous jaw, etc., careful explanation by a dentist will also be necessary. For example, if the tablet can be adhered to a location where it is dissolved by saliva without detaching for a relatively long time (6 hours or longer), it is basically considered that the efficacy of the drug can be ensured even if the use of dentures during the day can be continued. However, not just prescribing the drug, it is necessary to observe appropriate oral care and appropriate control of dentures such as detaching dentures at night, and for that purpose, collaboration with dentistry staff is essential. In addition, it is also necessary to avoid brushing and chewing of sticky substance such as gum during adhering the drug to mucosa because the adhesion sides of the drug to maxillary gingiva (canine fossa) should not be mistaken and the drug may become detached if it is touched even after adhesion. In case

### Table 8. Drug-related adverse events (≥ 2 subjects)

| System Organ Class                  | No. of subjects with drug-related AE (%) |
|-------------------------------------|-----------------------------------------|
|                                     | SO-1105 group (n = 62)                  | Gel group (n = 61)                        |
| Gastrointestinal disorders          | 5 (8.1)                                 | 4 (6.6)                                 |
| Abdominal discomfort                | 2 (3.2)                                 | 3 (1.6)                                 |
| Nausea                              | 2 (3.2)                                 | 4 (0.0)                                 |
| General disorders and               |                                         |                                         |
| administration site conditions      |                                         |                                         |
| Application site irritation         | 9 (14.5)                                | 11 (2.4)                                |
| Application site discomfort         | 1 (1.6)                                 | 2 (3.3)                                 |
| Nervous system disorders            | 6 (9.7)                                 | 7 (8.2)                                 |
| Dysgeusia                           | 5 (8.1)                                 | 6 (6.6)                                 |

* MedDRA-J Ver.17.1
that the drug becomes detached, it is necessary to adhere it again if it is within 6 hours after first adherence of the day, and not to adhere it again if it is 6 hours or longer after first adherence of the day and to adhere another tablet at the fixed time of the following day.

In this study, adverse drug reactions of the drug caused by the topical formulation such as dysgeusia and application site discomfort, and application site irritation and application site pain, which were infrequent though, were observed. However, all of them were mild and were improved during follow-up after treatment, and it is considered that the symptoms could have been mitigated by switching the location of adherence between left and right fossae every other day. If the amount of saliva is insufficient for the adhesive tablet due to dry mouth, etc., theoretically, the active ingredient may not spread throughout oral cavity and inflammation at the adhesive site may be more likely to occur. Furthermore, since the drug is the tablet to be used by adhere it to oral mucosa, it is also important for patients to fully understand that it should be used without swallowing, licking, or crushing.

The major benefit of for the drug is that the adhesive tablet for once-daily is easy to administer to elderly patients, especially who need care, compared to the existing topical drugs frequently administered. Furthermore, adhesive tablets are expected to prevail as one of a convenient medication along with orally disintegrating (OD) tablets in future.

Based on the above, it is considered that the introduction of SO-1105 into Japan will resolve the problems related to high frequency of administration of the existing topical therapeutic drugs (4-5 doses/day) and discomfort when using miconazole gel, and improve medication adherence and QOL in patients with OPC.

SO-1105 is considered to be widely used in clinical settings as a therapeutic drug for OPC.

Acknowledgments

Medical institutions or investigators other than the co-author who cooperated with this study are as follows.

Yamagata University Hospital (Mitsuyoshi Iino), Niigata University Medical & Dental Hospital (Ritsu Takagi), Gunma University Hospital (Satoshi Yokoo, Yu Takayama), University of Tsukuba Hospital (Hiroki Bukawa), Tokyo Dental College Ichikawa General Hospital (Takeshi Nomura, Kenichiro Ukichi, Homare Kawachi), The University of Tokyo Hospital (Hideto Saijo), Tokyo Medical University Hachioji Medical Center (Takashi Ogawa), Tokai University Hospital (Akihiro Kaneko), Yokohama City University Hospital (Iwai Tohnai), Osaka Rosai Hospital (Hideo Yoshioka), Kagoshima University Hospital (Kazumasa Sugiura).

Dr. Shinichi Watanabe of Teikyo University Hospital also provided us advice as the medical expert of the sponsor. We wish to take this opportunity to express our appreciation for Dr. Watanabe’s advice.

Conflicts of interest

The co-author, Masahiro Umeda, has received a research fund from Sosei Co. Ltd. after the acquisition of marketing authorization for SO-1105.

References

1) Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD: Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis 62: e1-50, 2016.
2) Vazquez JA, Sobel JD: Miconazole mucoadhesive tablets: a novel delivery system. Clin Infect Dis 54: 1480-1484, 2012.
3) Interview form FLORID® Oral gel 2%, Mochida Pharmaceutical Co. Ltd., 1, 2017.
4) Tanaka H: Use experience of florid gel oral use for oral mycosis. Comparison of deglutition and disorption methods. Prog Med 17: 1442-1446, 1997.
5) Lalla RV, Bensadoun RJ: Miconazole mucoadhesive tablet for oropharyngeal candidiasis. Expert Rev Anti Infect Ther 9: 13-17, 2011.
6) Murray PA, Koletar SL, Mallegol I, Wu J, Moskovitz BL: Itraconazole oral solution versus clotrimazole troches for the treatment of oropharyngeal candidiasis in immunocompromised patients. Clin Ther 19: 471-480, 1997.
7) Cardot JM, Chaumont C, Dubray C, Costantini D, Aiache JM: Comparison of the pharmacokinetics of miconazole after administration via a bioadhesive slow release tablet and an oral gel to healthy male and female subjects. Br J Clin Pharmacol 58: 345-351, 2004.
8) Interview form ORAVIT® Mucoadhesive Tablets 50 mg, Sosei Co. Ltd., 19-21, 2019.
9) Conditions of competition for milk protein products in the U.S. market - United States International Trade Commission - investigation No. 332-453, USITC Publication 3692: 1-7; 2004.