SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company</td><td>Daiichi Sankyo Co., Ltd.</td></tr>
<tr><td>Name of Finished Product</td><td>GRACEVIT ® TABLETS, GRACEVIT ® FINE GRANULES</td></tr>
<tr><td>Name of Active Ingredient</td><td>Sitafloxacin</td></tr>
<tr><td>Title of Study</td><td>Phase 3 clinical study of DU-6859a in patients with respiratory tract infection</td></tr>
<tr><td>Investigators</td><td>Dr. Hiroyuki Koba, and 42 other investigators</td></tr>
<tr><td>Study Centre(s)</td><td>43 sites</td></tr>
<tr><td>Publication (reference)</td><td>None</td></tr>
<tr><td>Studied Period</td><td>Date of obtaining first consent: October 14, 2008
Date of last observation: February 12, 2010</td></tr>
<tr><td>Phase of Development</td><td>Phase 3</td></tr>
<tr><td>Objectives</td><td>The aim of this study is to compare the safety, eradication rate of pneumococci, and PK-PD parameter at 100 mg once daily to those at 50 mg twice daily. Additionally, the bacteriological efficacy against drug-resistant pneumococci is evaluated.</td></tr>
<tr><td>Methodology</td><td>Open-label, multicentre, randomized study</td></tr>
<tr><td>Number of Patients
(planned and analyzed)</td><td>Planned: 150 patients
Analyzed:
We combined the data from the twice-daily 50 mg sitafloxacin treatment group in this study with the results from the same treatment group in the open study that was conducted in 2005 and 2006.
<table>
<tr><td rowspan="2">Treatment group</td><td rowspan="2">100 mg qd</td><td colspan="3">50 mg bid</td></tr>
<tr><td>This study</td><td>Previous study</td><td>Total</td></tr>
<tr><td>Valid for analysis of safety</td><td>98</td><td>51</td><td>115</td><td>166</td></tr>
<tr><td>Valid for analysis of efficacy</td><td>92</td><td>47</td><td>92</td><td>139</td></tr>
<tr><td>Valid for analysis of Streptococcus pneumoniae</td><td>56</td><td>25</td><td>16</td><td>41</td></tr>
<tr><td>Valid for analysis of PK-PD</td><td>53</td><td>24</td><td>16</td><td>40</td></tr>
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<tr><td>Diagnosis and Main Criteria for Inclusion</td><td>Diagnosis: Pneumococcal respiratory tract infections
Inclusion:
1) Patients with age of 20 or older at the time of obtaining informed consents.
2) Patients who provided proper sputum for cultivation of pathogenic bacteria.</td></tr>
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	3) Patients who is suspected to be pneumococcal infection with at least one of below**: (1) Neutrophils and Gram-positive diplococci can be seen in Gram stained smears of airway secreta (sputum etc.). (2) Urinary antigen detection test for *Streptococcus pneumoniae* is positive. ** (1) is essential for the patients received antibacterial drug within 7 days (14 days for azithromycin) from the start of therapy. 4) Patients who diagnosed as a mild or moderate infectious disease according to the guideline (Clinical evaluation methods for new antimicrobial agents to treat respiratory infections: Report of the Committee for the Respiratory System, Japan Society of Chemotherapy) on the day or the day before the start of therapy and fit for oral antibacterial drug therapy.
Test Product, Dose and Mode of Administration, Batch Number	100 mg QD group: Oral administration of DU-6859a at 100 mg, once daily 50 mg BID group: Oral administration of DU-6859a at 50 mg, twice daily DU-6859a lot No.: D6859F1S08T01A
Duration of Treatment	Seven days
Reference Therapy, Dose and Mode of Administration, Batch Number	None
Criteria for Evaluation	1) Incidence of adverse events and of adverse drug reactions 2) Bacteriological response against *S. pneumoniae* and drug-resistant *S. pneumoniae* 3) PK-PD parameter (*f*$AUC_{0\text{-}24h}$/MIC, *f*C_{max}/MIC, ratio of patients whose *f*C_{max} are over MPC, *f*Time inside MSW)
Statistical Method	As bacteriological response, incidence of adverse events, incidence of adverse drug reactions, and the ratio of patients whose C_{max} are over MPC, point estimation and the two-sided 95% confidence interval were calculated for both groups. Summary statistics of another PK-PD indices were calculated. We combined the data from the twice-daily 50 mg sitafloxacin treatment group in this study with the results from the same treatment group in the open study that was conducted in 2005 and 2006.

Summary - Conclusion	The eradication rate of *S. pneumoniae* was 98.2% (55/56) in 100 mg QD group and 92.7% (38/41) in 50 mg BID group, respectively. The eradication rate of multidrug-resistant *S. pneumoniae* was 97.7% (42/43) in 100 mg QD group and 94.6% (35/37) in 50 mg BID group. The mean *f*$AUC_{0\text{-}24h}$/MIC did not differ significantly between the 100 mg QD group (103.24) and the 50 mg BID group (105.25). The mean *f*C_{max}/MIC was higher in the 100 mg QD group (10.19) than in the 50 mg BID group (6.53). Pathogen eradication rate was 98.9% (89/90) when *f*$AUC_{0\text{-}24h}$/MIC was over 30. The eradication rate was also 98.9% (89/90) when *f*C_{max}/MIC was over 2. The incidence of adverse drug reactions was 33.7% (33/98) in 100 mg QD group and 40.4% (67/166) in 50 mg BID group. No obvious differences in efficacy and safety were observed between 100 mg QD group and 50 mg BID group. In case where a sufficiently high C_{max} needs to be ensured in view of the susceptibility of pathogens to drug, once daily 100 mg treatment should be selected.
Date of Report	March 26, 2012