Synopsis of Study Results

Name of Sponsor/Company	Daiichi Sankyo Company, Limited
Name of Finished Product (if approved)	Gabalon Intrathecal Injection
Name of Active Ingredient	baclofen
Title of Study	• Phase 3 Clinical Study of DL-404 (Baclofen Injection) Intrathecally Administered with MDT-3101 (implantable pump system) (long-term safety study) • Postmarketing Clinical Study of Baclofen Injection Administered with Implantable Pump System (extension study of clinical study)
Investigators	-
Study centers	10 medical institutions
Publications (of study results)	Not published
Studied period	Start date: August 23, 2002, the day after the day of final observations of the first patient in the preceding long-term maintenance treatment study (Japic CTI-050061) End date: January 26, 2007 (date of regulatory approval) Postmarketing clinical study: Only adult patients, April 12, 2005 (day after date of regulatory approval for adults) to April 30, 2006
Phase of development	Phase 3 (extention to phase 4)
Objectives	Therapeutic
Methodology	Multicenter, open-label study
Number of Patients (planned and analyzed)	Planned: 13 Analyzed: 24
Diagnosis and main criteria for inclusion	Disease: *Severe spastic paralysis of spinal origin* Spastic paralysis associated with spinal cord injury, multiple sclerosis, spinocerebellar degeneration (hereditary spastic paraplegia), spinal vascular disorder, ossification of posterior longitudinal ligament, or cervical spondylosis *Severe spastic paralysis of cerebral origin* Spastic paralysis associated with spastic cerebral palsy or head trauma Inclusion criteria: Male and female hospitalized patients and outpatients satisfying all of the

	following conditions will be included: 1） Responders as of the conclusion of the preceding long-term maintenance treatment study (Japic CTI-050061) found to pose no safety problems by the investigator or subinvestigator 2） Available for periodic follow-up during study period Exclusion criteria: None
Test product, dose and mode of administration, and batch number	The following 2 drug products were used as the investigational products: (1) DL-404 for injection, 5 mL ampoule (2 mg/mL), batch no. M01014-2A (2) DL-404 for injection, 20 mL ampoule (0.5 mg/mL), batch no. M01014-4A The patients continued to use the investigational device used in the preceding long-term maintenance treatment study (Japic CTI-050061). A device from among the following was selected if replacement was required: (3) 18 mL pump reservoir, model no. 8627L18 (4) 10 mL pump reservoir, model no. 8627L10 (5) One-piece catheter, model no. 8709 (6) Two-piece catheter, model no. 8711 (7) Programmer, model no. 8821 (8) Tunneling accessory, model nos. 8590-41, 859138, 859160 Doses and modes of administration: The initial dose in the study was the dose used at the conclusion of the preceding long-term maintenance treatment study (Japic CTI-050061). A dose increase was allowed once every 24 hours within the range of 40% of the immediately preceding dose of the investigational product for disease of spinal origin or 20% for disease of cerebral origin (including that in pediatric patients) as appropriate when dose adjustment for maintenance of efficacy was required. The upper limits for the daily dose were 1500 μg/day for disease of spinal origin, 1000 μg/day for disease of cerebral origin, and 800 μg/day for pediatric patients (16 years of age or younger). When required, dose reduction of the daily dose was allowed within the range of 20% of the immediately preceding dose.
Duration of treatment	Until regulatory approval of DL-404 and MDT-3101 for the respective diseases
Reference therapy, dose and mode of	

administration, and batch number	
Endpoints	*Efficacy endpoints* (1) Mean Ashworth score of 8 left and right lower extremity sites (2) Mean Ashworth score of 8 left and right upper extremity sites (only patients with severe spastic paralysis of cerebral origin) (3) Spasm score (except in patients with spastic cerebral palsy) (4) Kenny self-care score *Safety endpoints* (1) Adverse events (2) Adverse drug reactions to investigational product (i.e., adverse events for which causal relationship with investigational product was not ruled out) (3) Device-related problems (i.e., problems for which causal relationship with investigational device was not ruled out) (4) Concurrent events (i.e., events for which causal relationship with surgery, procedure, or refilling technique was not ruled out) (5) Vital signs and laboratory test results
Statistical methods	(1) Analysis populations All subjects without significant GCP noncompliance were included in the analyses. (2) Statistical methods for efficacy endpoints Pre- and post-treatment differences were determined for the Ashworth scores, Spasm scores, and Kenny self-care scores of each patient. Changes in mean Ashworth scores were calculated along with the 95% confidence intervals. (3) Statistical methods for safety endpoints Tables were prepared and incidences were calculated for the patients who suffered an adverse event, the patients who suffered an adverse drug reaction to the investigational product, the patients who suffered a device-related problem, the patients who suffered a concurrent event, and the patients who suffered an abnormal change.
Summary – Conclusions	*Efficacy Results* All 24 patients enrolled (19 adults and 5 children) were included in the analysis population. After the preceding long-term maintenance treatment study (Japic CTI-050061), the change (and 95% confidence internal) in mean Ashworth score for the 8 left and right lower extremity sites was 1.72 to 2.24 (1.24,

	2.51), which was a significant decrease indicating the anti-spasticity effect of DL-404 until 48 months. After the preceding long-term maintenance treatment study (Japic CTI-050061), the change (and 95% confidence interval) in mean Ashworth score for the 8 left and right upper extremity sites was 0.65 to 1.20 (0.06, 2.34), which was a significant decrease indicating the anti-spasticity effect of DL-404 until 45 months. After the preceding long-term maintenance treatment study (Japic CTI-050061), the change (and 95% confidence interval) in mean left and right spasm score was 1.33 to 1.76 (0.21, 2.62), which was a significant decrease indicating the anti-spasticity effect of DL-404 until 48 months. An assessment of patient independence according to Kenny self-care totals revealed no improvement. *Safety Results* Twenty-four of the 24 patients experienced 556 adverse events for an adverse event incidence of 100.0%. Although no deaths were reported, 8 of the patients suffered 14 other serious adverse events (including those in the postmarketing clinical study). Thirty-seven adverse events for which a causal relationship with the investigational product was not ruled out (adverse drug reactions) were reported in 13 of the 24 patients for an adverse drug reaction incidence of 54.2%. The adverse drug reactions were malaise, constipation, headache, pruritus, vomiting, increased blood CK, hypesthesia, peripheral coldness, nausea, dysuria, urinary retention, extrasystoles, asthenia, chest discomfort, pain, device-related discomfort, increased prostatic specific antigen, muscular weakness, urinary incontinence, epididymitis, prostatitis, and rash. The incidences of adverse drug reactions classified by underlying disease were 73.3% (35 occurrences in 11 of 15 patients) for disease of spinal origin (adults) and 50.0% (2 occurrences in 2 of 4 patients) for disease of cerebral origin (adults). No adverse drug reaction was reported for disease of cerebral origin (children). Eleven adverse events for which a causal relationship with the investigational device was not ruled out (device-related problems) were reported in 8 of the 24 patients for a device-related problem incidence of 33.3%. The problems reported were wound complication, implant site reaction, extrasystoles, pain, device-related discomfort, increased blood CK, hypesthesia, and rash. Seven adverse events for which a causal relationship with surgery, a

	procedure, or refill technique was not ruled out (concurrent events) were reported in 5 of the 24 patients for a concurrent event incidence of 20.8%. The concurrent events reported were device-related complication, device-related discomfort, wound complication, hypesthesia, and rash. For overall treatment (following pump implantation), with the preceding long-term maintenance treatment study and postmarketing clinical study combined, adverse event incidence was 100.0% (949 occurrences in 25 of 25 patients), adverse drug reaction incidence was 76.0% (73 events in 19 of 25 patients), device-related problem incidence was 52.0% (25 occurrences in 13 of 25 patients), and concurrent event occurrence was 32.0% (14 occurrences in 8 of 25 patients). *Conclusions* The study demonstrated a long-term anti-spasticity effect was maintained following the preceding long-term maintenance treatment study (Japic CTI-050061). None of the patients (24) enrolled in the study (and postmarketing clinical study) suffered any problematic severe adverse drug reaction. No adverse drug reaction was reported in the pediatric patients. No adverse drug reactions attributable to overdose or underdose were reported. The study showed that long-term safety was maintained following the previously conducted long-term maintenance treatment study (Japic CTI-050061). The daily dose beginning 6 months after pump implantation (including that in the postmarketing clinical study) was on average adjusted over a range of 172.61 to 271.30 μg/day. This range classified by the underlying disease was on average 205.44 to 295.16 μg/day for disease of spinal origin (adults), 94.16 to 140.06 μg/day for disease of cerebral origin (adults), and 98.56 to 198.65 μg/day for disease of cerebral origin (children).
Date of the synopsis	2011 / 07 / 30