A POST MARKETING SURVEILLANCE SURVEY OF DYSPORT FOR EVALUATING SAFETY OF DYSPORT IN KOREAN PATIENTS SUFFERING FROM SPASTICITY OR DYSTONIA

SURVEY PROTOCOL

SURVEY number: A-38-52120-114
PRODUCT NAME: Dysport

Final Version 3, Dated: 13th September 2006

Sponsor's Medically Responsible Person: :

PPD
Ipsen Korea
13th FL., Seshin Bldg., 129-11
Cheongdam-Dong, Gangnam-Gu, Seoul
Korea
Tel: PPD
Fax: PPD

Sponsor's Co-ordinating & Monitoring Office:

PPD
Ipsen Korea
13th FL., Seshin Bldg., 129-11
Cheongdam-Dong, Gangnam-Gu, Seoul
Korea
Tel: PPD
Fax: PPD

Pharmacovigilance/Emergency contact

PPD
Ipsen Korea
13th FL., Seshin Bldg., 129-11
Cheongdam-Dong, Gangnam-Gu, Seoul
Korea
Tel: PPD
Fax: PPD

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the **A POST MARKETING SURVEILLANCE SURVEY OF DYSPORT FOR EVALUATING SAFETY OF DYSPORT IN KOREAN PATIENTS SUFFERING FROM SPASTICITY OR DYSTONIA.** I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)[1], local regulations (as applicable) and the survey protocol. I agree to conduct the survey according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the survey.

NAME:
TITLE: <PRINCIPAL INVESTIGATOR: SIGNATURE: _____

DATE: _____

OFFICE:

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

On behalf of the Sponsor:

NAME: PPD
TITLE: PPD SIGNATURE: _____

DATE: _____

OFFICE: Ipsen Korea

[1] ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996.

SYNOPSIS

Survey Title:	A post marketing surveillance survey of Dysport for evaluating safety of Dysport in Korean patients suffering from Spasticity or Dystonia
Survey Objectives:	To provide a further assessment of the risk/benefit of Dysport as a marketed product
Phase of Trial:	Post Marketing Survey
Survey Design:	Investigators will prescribe Dysport according to their normal practice. Each investigator will record the dose of Dysport administered and the condition being treated. At the patients scheduled return to the site (following visit depends on investigator's judgement, it's usually about 4 weeks later), their treating physician will perform an assessment of safety, and details on any adverse events will be collected. Patients who do not return to site will be contacted by telephone to ask about any adverse events that they have had since their treatment.These data will be recorded on simple Case Record Forms (CRFs) and returned to Ipsen.
Survey Population:	Reports on about 500 patients will be collected.
Survey Treatment:	**Survey Product:** The medication under investigation is Dysport®, in unopened vials to be kept at temperatures between 2°C and 8°C DYSPORT® is presented as a white freeze-dried pellet containing nominally 500 Units of Clostridium botulinum type A toxin-haemagglutinin complex together with 125 µg of human albumin and 2.5 mg of lactose in a clear glass vial. Dysport will be purchased by the centre participating in this post marketing surveillance survey and will be reconstituted at the clinic with sterile physiological saline for injection without preservative according to the SmPC and should be used within eight hours after reconstitution. The treating physician according to the condition being treated will decide the dose and sites of injection, as described in the SmPC.
Survey Evaluations:	**Efficacy Evaluation(s):** **None** **Safety Evaluations:** Monitoring of adverse events (AEs). **Pharmacokinetic Evaluations:** **None**

	Pharmacodynamic Evaluations: **None**
Statistical Methods:	The sample size of 500 is based on feasibility and not on any statistical considerations. In terms of study reporting, the analysis will be descriptive: data summaries will consist of descriptive statistics like counts, means, standard deviations, medians, minima, maxima or frequencies / percentages as appropriate. The safety analysis will be based on the safety population (defined as all treated patients).

TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event/Experience
CA	Competent Authorities
CDDS	Clinical Development Data Sciences (relates to Sponsor)
CRF	Case Report Form
CRO	Contract Research Organisation
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Survey medication	Investigational Medicinal Product synonymous with "study drug"
IRB	Institutional Review Board
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
PC	Prostate Cancer
RAP	Reporting and Analysis Plan
SAE	Serious Adverse Event/Experience
SAS®	Statistical Analysis System®
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent Adverse Event
TMF	Trial Master File

2. INTRODUCTION

2.1 Disease Review

Not Applicable (N/A)

2.2 Compound Review

Dysport is the formulation of *Clostridium botulinum* type A toxin-hemagglutinin complex manufactured by Ipsen. It is currently available commercially in over 60 countries. It is registered for the treatment of blepharospasm, hemifacial spasm, cervical dystonia, post stroke arm spasticity, post stroke leg spasticity, cerebral palsy equinus foot spasticity, hyperhidrosis and glabellar wrinkles although not all indications are approved in all countries.

2.3 Clinical Survey Rationale

This is a post marketing survey to collect safety data based on routine treatment of subjects with Spasticity or Dystonia.

3. SURVEY OBJECTIVES

3.1 Primary Survey Objective

To provide a further assessment of the risk / benefit of Dysport as a marketed product.

3.2 Secondary Survey Objectives

none

4. SURVEY DESIGN

4.1 Overview

Centers will prescribe Dysport according to their normal practice. Each center will record the dose of Dysport administered and the condition being treated. At the patients scheduled return to the site (following visit depends on investigator's judgement, it's usually about 4 weeks later), their treating physician will perform an assessment of safety, and details on any adverse events will be collected. Patients who doesn't return to site will be contacted by telephone to ask about any adverse events that they have had since their treatment.These data will be recorded on simple Case Record Forms (CRFs) and returned to Ipsen.

4.1.1 Population Characteristics

Patients with Spasticity or Dystonia scheduled to receive Dysport within each participating centre are to be included in this survey.

4.1.2 Design

This is an open, non-randomised, multi-centre, non-interventional, post-marketing survey.

4.2 Endpoints

4.2.1 Efficacy Endpoints

None

4.2.2 Safety Endpoints

Collection of adverse events.

4.3 Justification of Design

The aim of the survey is to provide additional risk / benefit information on the use of Dysport within the specifications of the SmPC. The survey is therefore non-interventional, and is designed only to collect data that would normally be available in the standard treatment of patients with Dysport within licensed indications. As such, no additional measures of efficacy or safety are being collected other than those recorded in normal practice.

4.3.1 Survey Duration

The recruitment period will be approximately 4 months. Follow-up of patients will be dependent on each centre's normal practice and the indication treated. The duration of the survey for each subject will be a maximum of 16 weeks (4 months). The overall duration of the survey will be 8 months.

The survey will be considered to have started at first subject inclusion. It will be considered to have finished at normal follow-up visit interval after last Dysport intake.

5. COMPLIANCE WITH GOOD CLINICAL PRACTICE, ETHICAL CONSIDERATIONS & INFORMED CONSENT

5.1 Compliance with Good Clinical Practice and Ethical Considerations

NA.

According to Korea Food Drug Administration (KFDA) guideline, the followings are not the scope of clinical trial approval of KFDA. Therefore Compliance with Good Clinical Practice and Ethical Considerations are not applicable for Post marketing surveys based on Korean regulation.

- Studies for investigation of adverse event and observation of clinical efficacy of the already-marketed product with the already – approved label.
- Studies of the already-marketed product not for safety and efficacy data collection or not for commercial use
- Studies of the already-marketed product for developing the treatment of life-threatening disease which has no standard therapy nor alternative therapy
- Studies of In-Vitro diagnostics or quasi-drug
- Studies of the already marketed drug with other cases which KFDA commissioner admits.

*Pharmaceutical affairs act reinforcement regulations (amended at 2005 Jun 8)

5.2 Informed Consent

NA

Refer to section 5.1

6. SURVEY POPULATION

6.1 Subject Identification Code List and Number of Subjects

Each Investigator will maintain a record of all subjects enrolled into the survey.

This record called Subject Identification Code List should be kept confidential at the survey centre and should contain the centre number, subject number, subject name, subject initials, and telephone number.

It is planned to recruit approximately 500 subjects in approximately 20 centres in Korea.

6.2 Inclusion Criteria

All subjects must fulfil the following:

1) Subjects with indication disease scheduled to receive Dysport as per normal treatment practice, and in respect with Dysport SmPC.
2) Adult or child over the age of 2 years

6.3 Exclusion Criteria

Subjects will not be included in the survey if :

1) Subject has hypersensitivity to Dysport or drugs with a similar chemical structure.
2) Treatment with any other investigational drug within the last 30 days before survey entry.

6.4 Discontinuation/Withdrawal Procedures

N/A

7. METHODOLOGY

7.1 Survey Schedule

The schedule of observations and assessments during the survey are summarised below.

Table 1. Schedule of Observations

	Day 0	Follow-up visit	Telephone contact if no follow up visit

Demography& Eligibility	X		
Treatment injections	X		
Adverse events		X	X

7.2 Survey Visits

7.2.1 Baseline (Day 0, visit 1)

All subjects attending the centre for their normal Dysport treatment will receive Dysport as decided by the treating physician, in accordance with the marketing authorisation. The following details will be recorded on the survey CRF:

- Centre number
- Subject number
- Subject initials,
- Demography
- Previous Toxin history
- Indication
- Dysport administration

7.2.2 Follow-up visit

Patients will then return for their normal follow up visit and an assessment of safety will be recorded on the CRF along with any AEs that have occurred since the last treatment.

- Collection of adverse events

7.2.3 Telephone contact

Contact will be made with the patient by telephone after planned normal follow-up visit, or if the patient is unavailable to visit. Patients will be asked about any AEs that they may have experienced since they received their Dysport treatment. These AEs will be recorded on the CRF.

7.2.4 Survey Completion or Withdrawal

N/A

8. SURVEY EVALUATIONS

8.1 Efficacy Endpoints and Evaluations

None

8.1.1 Primary Efficacy Endpoint and Evaluations

None

8.1.2 Secondary Efficacy Endpoints and Evaluations

None

8.2 Safety Endpoints and Evaluations

8.2.1 Adverse Events

AEs will be collected from the first treatment administration to the end of the follow-up period. AEs will be elicited by direct, non-leading questioning or by spontaneous reports. Further details for AE reporting can be found in Section 10.

9. SURVEY TREATMENTS

9.1 Survey Treatments Administered

Administration of Dysport will be supervised by the Investigator, or designee.

Survey medication

Chemical name:	*Clostridium botulinum* type A toxin-hemagglutinin complex
Survey Code:	Dysport
Dosage form:	Powder for dilution and injection
Strength:	500 units
Manufacturer:	Ipsen Biopharm Ltd., Wrexham, United Kingdom (UK)
Description:	Dysport is supplied as a white, lyophilized powder containing 500 units of *Clostridium botulinum* type A toxin-haemagglutinin complex, 125 μg human serum albumin, and 2.5 mg of lactose. The product will be reconstituted at the investigational sites with sterile physiologic saline for injection without preservative.

9.2 Subject Identification and Allocation to Survey Treatment

All subjects enrolled must be identifiable throughout the survey. The Investigator will maintain a list of subject numbers and names to enable records to be found at a later date if required. This record called Subject Identification Code List should be kept confidential at the survey centre.

The subject number will be allocated at baseline visit following the chronological order of the subject entry into the survey at a particular site. Subjects will be identified using a unique subject identification during the survey: site number + subject number. Subject number and site number will be noted in the CRF.

9.2.1 Randomisation

NA

9.2.2 Blinding, Emergency Envelopes and Breaking the Blind

NA

9.3 Survey Treatment Supply

The centre will purchase Dysport vials, each bearing a unique lot number, by their normal method. The Dysport is the commercially available material in the country.

Centres will prescribe Dysport according to their normal practice and in respect to the SmPC.

9.4 Compliance

NA

9.5 Survey Treatment Storage

Until dispensed to the patients, Dysport will be stored refrigerated, as is the custom at the hospital/practice.

9.6 Concomitant Medication/Therapy

NA

10. ADVERSE EVENT REPORTING

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g. nausea, chest pain), signs (e.g. tachycardia, enlarged liver) or the abnormal results of an investigation (e.g. laboratory findings, electrocardiogram). In clinical studies an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no survey treatment has been administered.

This definition includes events occurring from the time of the subject receiving the first administration of Dysport until the end of the survey.

10.1 Disease Progression

NA

10.2 Categorisation of Adverse Events

10.2.1 Intensity Classification

AEs will be classified as mild, moderate or severe according to the following criteria:

Mild:	symptoms do not alter the subject's normal functioning
Moderate:	symptoms produce some degree of impairment to function, but are not hazardous, uncomfortable or embarrassing to the patient
Severe:	symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

10.2.2 Causality Classification

The relationship of an AE to the Survey medication will be classified according to the following:

Related:	reports including good reasons and sufficient information (e.g. plausible time sequence, dose-response relationship, pharmacology, positive de-challenge and/or re-challenge) to assume a causal relationship with the Survey medication in the sense that it is plausible, conceivable or likely.
Not related:	reports including good reasons and sufficient information (e.g. implausible time sequence and/or attributable to concurrent disease or other drugs) to rule out a causal relationship with the Survey medication.

10.2.3 Assessment of expectedness

NA

10.2.4 Laboratory Test Abnormalities

NA

10.2.5 Abnormal Physical Examination Findings

NA

10.2.6 Other Investigation Abnormal Findings

NA

10.3 Recording and Follow-up of Adverse Events

At each visit the patient should be asked a non-leading question such as: "Do you feel different in any way since starting the new treatment/the last assessment?"

All observed or volunteered AEs, regardless of treatment group or suspected causal relationship to Survey medication, will be recorded on the AE page(s) of the CRF. Events involving drug reactions, accidents, illnesses with onset during the treatment phase of the survey, or exacerbation's of pre-existing illnesses should be recorded.

AEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.

For all AEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor or its designated representative. For all AEs, sufficient information should be obtained by the Investigator to determine the causality of the AE (i.e., Survey medication or other illness). The Investigator is required to assess causality and record that assessment on the CRF. Follow-up of the AE, after the date of therapy discontinuation, is required if the AE or its sequelae persist. Follow-up is required until the event or its sequelae resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.

10.4 Serious Adverse Events

10.4.1 Definitions

All SAEs (as defined below) regardless of treatment group or suspected relationship to Survey medication must be reported immediately (within 24 hours of the Investigator's knowledge of the event) to the pharmacovigilance contact specified at the beginning of this protocol. If the immediate report is submitted by telephone, this must be followed by detailed written reports using the SAE report form.

A SAE is any AE occurring at any dose that:

1. results in death;
2. is life threatening, that is any event that places the patient at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death;
3. results in in-patient hospitalisation or prolongation of existing hospitalisation, excluding admission for social or administrative reasons (see further);
4. results in a persistent or significant disability/incapacity, where disability is a substantial disruption of a person's ability to conduct normal life functions;
5. results in congenital anomaly/birth defect in the offspring of a patient who received the Survey medication;
6. is an important medical event that may not result in death, be life-threatening, or require hospitalisation when, based upon appropriate medical judgement, may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalisation, or the development of drug dependency or drug abuse.

Regardless of the above criteria, any additional AE that the Sponsor or an Investigator considers serious should be immediately reported to the Sponsor and included in the corporate SAEs database system.

- **Hospitalisation** is defined as any in-patient admission (even if less than 24 hours). For chronic or long-term in-patients, in-patient admission also includes transfer within the hospital to an acute/intensive care in-patient unit.
- **Prolongation of hospitalisation** is defined as any extension of an in-patient hospitalisation beyond the stay anticipated/required in relation to the original reason for the initial admission, **as determined by the Investigator or treating physician**. For protocol-specified hospitalisation in clinical trials, prolongation is defined as any extension beyond the length of stay described in the protocol. Prolongation in the absence of a precipitating, treatment-emergent, clinical AE (i.e., not associated with the development of a new AE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not patient to immediate reporting to the Sponsor.
- Pre-planned or elective treatments/surgical procedures should be noted in the patient's screening documentation. Hospitalisation for a pre-planned or elective treatment/surgical procedure should not be reported as an SAE unless there are complications or sequelae which meet the criteria for seriousness described above.

10.4.2 Reporting Requirements

In this Post Marketing Survey only Related Serious Adverse Events will be reported immediately (within 24 hours) by Investigator to sponsor on the Clinical Study Serious Adverse Events forms. All other SAEs will be reported on the AE forms of the CRF.

10.4.3 Mandatory Information for Reporting Related SAE

The following information is the minimum that must be provided to the Sponsor pharmacovigilance contact within 24 hours for each SAE:

- Trial number
- Centre number
- Subject number
- AE
- Investigator's name and contact details

The additional information included in the SAE form must be provided to the Sponsor or representative as soon as it is available. Upon receipt of the initial report, the Sponsor will ask for the Investigator's causality assessment if it was not provided with the initial report.

The Investigator should report a diagnosis or a syndrome rather than individual signs or symptoms. The Investigator should also try to separate a primary AE considered as the foremost untoward medical occurrence from secondary AEs which occurred as complications.

10.5 Pregnancy

Pregnancy is not a criterion of seriousness. However, any unintended pregnancy occurring during treatment with the survey drug should be reported in the same timelines as an SAE, using the pregnancy reporting form. The

investigator/monitoring physician will be instructed by the sponsor in the tracking of the pregnancy outcome (a special form to obtain the information required will be sent to the monitoring physician).

A female patient must be instructed to stop taking the survey drug and immediately inform the investigator if she becomes pregnant during the survey. The investigator should report all pregnancies to the sponsor within 24 hours of becoming aware of them. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the fœtus. Monitoring of the subject should continue until conclusion of the pregnancy.

10.6 Deaths

All AEs resulting in death either during the survey period or within 28 days after the last dose of Survey medication must be reported as an SAE within 24 hours of the Investigator's knowledge of the event.

The convention for recording death is as follows:

- AE term: lead cause of death (e.g. multiple organ failure, pneumonia, myocardial infarction).
- Outcome: fatal.
- The **only exception** is if the cause of death is unknown (i.e. sudden or unexplained death), in which case the AE term may be 'Death' or 'Sudden death'.

10.7 Discontinuation/Withdrawal due to Adverse Events/Serious Adverse Events

Discontinuation/withdrawal due to AEs should be distinguished from discontinuation/withdrawal due to insufficient response to the Survey medication (see Sections 6.4.).

If the Survey medication is discontinued due to a SAE it must be reported immediately to the Sponsor's designated representative (see Section 10.4).

In all cases the Investigator must ensure the subject receives appropriate medical follow-up.

10.8 Reporting to Competent Authorities/IECs/IRBs/Other Investigators

The Sponsor will ensure that processes are in place for submission of reports of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the survey to the Competent Authorities (CA), IECs, IRBs and other Investigators concerned by the Survey medication. Reporting will be done in accordance with the applicable regulatory requirements.

11. STATISTICAL CONSIDERATIONS

11.1 Subject Classification and Definitions

- **Treated subject :** Subject who is treated with at least one dose of survey medication

11.2 Analyses Populations Definitions

- **Safety population:** All subjects who received at least one dose of survey medication

11.2.1 Populations Analysed

The analyses of safety data will be performed based on the Safety population.

11.3 Sample Size Determination

This is a Post Marketing Survey with a number of subjects where sample size of 500 was chosen on the basis of practical constraints and not on statistical considerations. Therefore, it is not intended to serve as the basis for definitive conclusions about safety or efficacy.

11.3.1 Significance Testing and Estimations

As this is a descriptive (safety and tolerability) survey, no statistical testing will be carried out.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed by an external Contract Research Organisation (CRO), managed by the Sponsor's Clinical Development Data Sciences Department.

A Reporting and Analysis plan (RAP) describing the planned statistical analysis in detail with tables, figures and listings (TFLs) templates will be developed as a separate document.

Statistical evaluation will be performed using Statistical Analysis System (SAS)®.

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) or demographic and previous toxin medication history will be presented.

11.4.2 Subject Disposition and Withdrawals

The numbers of subjects who were treated, discontinued and completed the survey period will be tabulated. Primary reasons for discontinuation of survey treatment will be tabulated.

11.4.3 Pharmacokinetic Data

NA

11.4.4 Efficacy Evaluation

NA

11.4.5 Safety Evaluation

All safety data will be displayed in the subject data listings. Analyses and summary tables will be based upon the safety population.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term and system organ class. AE listings will be presented by subject, system organ class and preferred term.

Incidence of all reported AEs/treatment emergent AEs (TEAE) and SAEs will be tabulated. In addition, summary tables will be presented by maximum intensity, drug relationship and AEs/TEAEs associated with premature withdrawal of survey medication.

A TEAE is defined as any AE that occurs during the active phase of the survey if:

it was not present prior to receiving the first dose of Survey medication, or

it was present prior to receiving the first dose of Survey medication but the intensity increased during the active phase of the survey, or

it was present prior to receiving the first dose of Survey medication, the intensity is the same but the drug relationship became related during the active phase of the survey.

Treatment emergent AEs will be flagged (*) in the AEs listings.

Concomitant medication will be coded by using WHO Drug Dictionary and will be summarised with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

11.5 Subgroup Analyses

NA

11.6 Interim Analyses and Data Monitoring

NA

11.7 Final Analysis

NA

12. MONITORING PROCEDURES

The Investigator is responsible for the validity of all data collected at the site. The Sponsor is responsible for monitoring this data to verify that the rights and well being of subjects are protected, that trial data are accurate (complete and verifiable to source data) and that the trial is conducted in compliance with the protocol, GCP and regulatory requirements.

12.1 Routine Monitoring

Sponsor-assigned monitors or representatives will conduct regular site visits. The Investigator will allow direct access to all relevant files (for all subjects) for the purpose of verifying entries made in the CRF and assist with the monitor's

activities, if requested. Adequate time and space for monitoring visits should be made available by the Investigator.

Whenever a subject name is revealed on a document required by the Sponsor (e.g., laboratory print-outs) the name must be blacked out permanently by the site personnel, leaving the initials visible, and annotated with the subject number as identification.

13. SURVEY MANAGEMENT

13.1 Inspections and Auditing Procedures

Authorised personnel from external CAs and Sponsor-authorised Quality Assurance personnel may carry out inspections and audits. The purpose of an audit is to ensure that ethical, regulatory and quality requirements are fulfilled in all studies performed by the Sponsor.

Auditors and inspectors must have direct access to survey documents and site facilities as specified in section 12.1, and to any other locations used for the purpose of the survey in question (e.g., laboratories).

In the event of the site being notified directly of a regulatory inspection, the Investigator must notify the Sponsor representative as soon as possible, to assist with preparations for the inspection.

13.2 Data Recording of Survey Data

In compliance with GCP, the medical records/medical notes, etc., should be clearly marked and permit easy identification of a subject's participation in the specified clinical survey.

The Investigator must record all data relating to protocol procedures, Survey medication administration, safety data and on the CRFs provided for the survey. The Investigator, by completing the signature log, may formally designate authority to complete CRFs to appropriately qualified staff.

The Investigator must sign the End of Survey/ Certification of completion CRF page to attest to the accuracy and completeness of all the data.

All corrections on a CRF and on source documents must be made in a way, which does not obscure the original entry. The correct data must be inserted, dated and initialled/authorised by survey site personnel. If it is not obvious why a change has been made, a reason must be provided.

13.3 Source Data Verification

As required by GCP, the Sponsor assigned monitor must verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the CRF.

The source documents must, as a minimum, contain the following; a statement that the subject is included in a clinical survey, the identity of the survey, diagnosis and eligibility criteria, visit dates (with subject status), Survey medication administration, and any AEs and associated concomitant medication.

Definition for source data and source documents are given below:

13.4 Data Quality

Monitored CRFs transferred from the investigational site to the assigned Data Management group will be reviewed (secondary monitoring) for completeness, consistency, legibility and protocol compliance.

Reasons should be given on the relevant CRF page for any missing data and other protocol deviations, where space has been provided. Any data management queries and items not adequately explained will be returned to the Investigator by the monitor for clarification/correction. The Investigator must ensure that data queries are dealt with promptly. Copies of all data changes and clarifications must be retained by the Investigator and filed with the CRFs.

13.5 Data Management

Data management will be conducted by a CRO, directed by the Sponsor's Biometrics Group. All data management procedures will be completed in accordance with the CRO's SOPs and IPSEN's requirement.

The Sponsor will ensure that appropriate data entry methods are used (e.g., double data entry) and suitable queries are raised to resolve any missing or inconsistent data.

The Biometrics Group will also ensure that SAE data collected in the CRF is consistent with information provided to the sponsor's pharmacovigilance department (and vice versa).

The coding of an AE, medical history and concomitant medication terms will be performed by the contracted CRO / a CRO, directed by the Sponsor's CDDS Group, and reviewed and approved by the Sponsor. Concomitant medications will be coded using WHODRUG and AEs terms will be coded using MedDRA.

13.6 Survey Management Committees

NA

13.6.1 Data Monitoring Committee

NA

13.6.2 Steering Committee or Operations Committee

NA

13.7 Record Archiving and Retention*

The sponsor, or other owners of the data, shall retain all of the sponsor-specific essential documents pertaining to the trial for five years. The sponsor shall retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor shall maintain all sponsor-specific essential documents for at least 5 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

The sponsor shall inform the investigator(s)/institution(s) in writing of the need for record retention and shall notify the investigator(s)/institution(s) inwriting when the trial related records are no longer needed.

* Korea Food and Drug Administration Notification No. 1999-67; KGCP 29

14. ADMINISTRATION PROCEDURES

14.1 Regulatory Approval

As required by local regulations, the Sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to survey initiation in regions where an approval is required.

14.2 Publication Policy

The Sponsor encourages acknowledgement of all individuals/organisations involved in the funding or conduct of the survey, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this survey may be published or communicated to scientific meetings by the Investigators involved in the survey. For multicentre surveys, a plan for scientific publication and presentation of the results may be agreed and implemented by the survey Investigators or a Steering Committee. The Sponsor requires that reasonable opportunity be given to review the content and conclusions of any abstract, presentation, or paper before the material is submitted for publication or communicated. This condition also applies to any amendments that are subsequently requested by referees or journal editors. The Sponsor will undertake to comment on the draft documents within the time period agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or the author's institution). Requested amendments will be incorporated by the author, provided they do not alter the scientific value of the material.

If patentability would be adversely affected by publication, this will be delayed until (i) a patent application is filed for the content of the publication in accordance with applicable provisions of the clinical trial agreement concerned, (ii) the Sponsor consents to the publication, or (iii) the time period as may be agreed in the contractual arrangements, including clinical trial agreements, governing the relationship between the Sponsor and authors (or authors' institution) after receipt of the proposed publication by the Sponsor, whichever of (i), (ii) or (iii) occurs first.

The author undertakes to reasonably consider the Sponsor's request for delay to the proposed publication should the Sponsor reasonably deem premature to publish the results obtained at the then stage of the survey.

14.3 Clinical Survey Report

A final clinical survey report will be prepared according to the ICH guideline on structure and contents of clinical survey reports, regardless of whether the survey is completed or prematurely terminated. Where appropriate an abbreviated report may be prepared. The CSR will be in compliance with any applicable regulatory requirements, national laws in force and will be in English.

14.4 Contractual and Financial Details

The Investigator (and/or, as appropriate, the hospital administrative representative) and the Sponsor will sign a clinical survey agreement prior to the start of the survey, outlining overall Sponsor and Investigator responsibilities in relation to the survey.

14.5 Insurance, Indemnity and Compensation

NA

15. PROTOCOL AMENDMENTS

In the event that an amendment to this protocol is required, is will be classified into one of the following three categories:

- ***Non-Substantial Amendments*** are those that are not considered 'substantial' (e.g. administrative changes) and as such only need to be notified to the IECs/IRBs or Competent Authorities (CA) for information purposes.
- ***Substantial Amendments*** are those considered 'substantial' to the conduct of the clinical trial where they are likely to have a significant impact on:
    - the safety or physical or mental integrity of the subjects;
    - the scientific value of the trial;
    - the conduct or management of the trial; or
    - the quality or safety of the Survey medication used in the trial.

  Substantial amendments must be notified to the IECs/IRBs and CA. Prior to implementation, documented approval must be received from the IECs/IRBs. In the case of the CA in the EU member states, approval or 'favourable opinion' can be assumed if the CA has raised no grounds for non-acceptance during an allocated time period (to be confirmed with the Sponsor's Regulatory Affairs (RA) representative) following acknowledgment of receipt of a valid application to make a substantial amendment.
- ***Urgent Amendments*** are those that require urgent safety measures to protect the trial subjects from immediate hazard and as such may be implemented immediately by the Sponsor with subsequent IECs/IRBs and CA notification, forthwith.