POST MARKETING SURVEILLANCE (NON-INTERVENTIONAL STUDY) FOR EVALUATING THE EFFICACY AND SAFETY OF DYSPORT CZECH PATIENTS SUFFERING FROM POST-STROKE ARM SPASTICITY

STUDY PROTOCOL

Study number: A-38-52120-113-PMS
PRODUCT NAME: Dysport

Final Version 4.0 dated: 13th February 2012

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PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the **A POST MARKETING SURVEILLANCE (NON-INTERVENTIONAL STUDY) FOR EVALUATING THE EFFICACY AND SAFETY OF DYSPORT CZECH PATIENTS SUFFERING FROM POST-STROKE ARM SPASTICITY.** I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP)[1], local regulations (as applicable) and the Study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the Study.

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: **Milan Šikut, MD**
TITLE: Medical Director SIGNATURE: _____

DATE: _____

OFFICE: Ipsen Pharma, Prague

[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

Study Title:	A post marketing surveillance (non-interventional study) for evaluating the efficacy and safety of Dysport Czech patients suffering from Post-Stroke Arm Spasticity
Study Objectives:	To provide a further assessment of the risk/benefit of Dysport as a marketed product
Phase of Study:	Post Marketing Study (non-interventional study)
Study Design:	Centres will prescribe Dysport according to their usual practice and within the latest approved Summary of Product Characteristics (SmPC). (Last approved version dated 30.06.2008, ref.nr.6324/2007;24731/2008;35386/2008). Each center will record the treated muscles and the dose of Dysport administered. At visits during following year (5 visits assumed) prescriber will evaluate treatment success and administration interval and fullfil simple Case Record Form (CRF). Based on the subject interview, the prescriber will fulfil the DAS QOL questionnaire and in case of related AE, the AE reporting forms. Both will be returned to Ipsen.
Study duration	"Recruitment" period will be 18 months. Duration of Study is approximately one year per subject (three injections expected within 1 year according to SmPC)
Study Population:	Reports on up to 200 male or female adult subjects will be collected. **Study Inclusion Criteria** All subjects must fulfil the following: • Subjects with stroke either haemorrhagical or ischemic origin and stroke onset at least 3 months prior to study entry scheduled to receive Dysport. • Adults over the age of 18 years • Arm spasticity with Modified Ashworth scale ≥ 2 at least in one part **Study Exclusion Criteria** Subjects presenting with any of the following will not be included in the Study: • Hypersensitivity to any Dysport ingredient • Pregnancy • Previous administration of botulinum toxin

Study Treatment:	**Investigational Medicinal Product (IMP):** Dysport, botulinum toxin A, presented in a form of lyophilizate injections is used for several indications including post stroke arm spasticity of adults. The pack contains 1 or 2 glass vials with lyophilizate and should be reconstituted with 0,9 % NaCl before administration. The dosage will be set by physician according to SmPC. The maximal dose will be 1000 U per session.
Study Evaluations:	**Primary Efficacy Endpoint and Evaluation:** Global assessment of spasticity (Modified Ashworth scale) **Secondary Efficacy Endpoints and Evaluations:** Patient´s Quality of Life (QOL) evaluation (DAS scale) Interval between separate administration sessions **Safety Endpoints and Evaluations:** Monitoring of treatment related adverse events (RAEs). **Pharmacokinetic Endpoints and Evaluations:** None **Pharmacodynamic Endpoints and Evaluations:** None
Statistical Methods:	In terms of study reporting, the statistical analysis will be only descriptive: data summaries will consist of summary statistics like counts, mean, standard deviations, medians, minima, maxima or frequencies / percentages as appropriate. ITT / safety population will be used to describe all efficacy data and safety data.

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1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

RAE	Related Adverse Event
CA	Competent Authorities
CDDS	Clinical Development Data Sciences (relates to Sponsor)
CRF	Case Report Form
CRO	Contract Research Organisation
DAS	Disability Assessment Scale
EU	European Union
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
STUDY medication	Investigational Medicinal Product synonymous with "study drug"
IRB	Institutional Review Board
ITT	Intention to Treat
MedDRA	Medical Dictionary for Regulatory Activities
QOL	Quality of Life
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
AIFP	Association of Innovative Pharmaceutical Industry
SUKL	State Institute for Drug Control

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 Study Rationale

Non-interventional studies include the continuous evaluation that takes place after regulatory approval, when the drug is already on the market and available for general use. These studies are designed to monitor effects of selected medical treatments in routine use without direct influence on standard clinical practice.

The intention of this non-interventional study is to collect safety data, efficacy data, treatment interval and quality of life based on routine treatment of subjects with Post-Stroke Arm Spasticity.

3. STUDY OBJECTIVES

3.1 Primary Study Objective

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

3.2 Secondary Study Objectives

To provide quality of life assessment and to gather exploratory data on the interval between treatment injections.

4. STUDY DESIGN

4.1 Overview

Centres will prescribe Dysport according to their usual practice and within the Summary of Product Characteristics (SmPC). Latest approved version ref.nr. 6324/2007,24731/2008,35386/2008 is dated 30.06.2008. Each center will record the treated muscles and the dose of Dysport administered. Before the first administration and 4 weeks after that, prescriber will evaluate treatment success and will assess quality of life in the range of routine practice (if available). According to SmPC, 3 Dysport injections are expected within 1 year. During all visits performed

within a year, simple Case Record Form (CRF) will be fulfilled. In case of treatment related AE, the AE reporting forms will be fulfilled. Both will be returned to Ipsen.

4.1.1 Population Characteristics

Adult subjects with Post-Stroke Arm Spasticity newly scheduled to receive Dysport, with stroke onset at least 3 months prior to study entry, within each participating centre are to be included in this Study. All subjects should rehabilitate under professional inspection at the same time.

A total of 200 subjects are expected to be recruited.

4.1.2 Design

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

Subject will be asked to provide a written informed consent. Inclusion & exclusion criteria will be checked prior to study enrolment.

Modified Ashworth scale and DAS scale will be evaluated before the first Dysport injection and 4 weeks after it, if available according to routine practice.

During one year, investigator will count-up real administration interval between treatment injections.

4.2 Endpoints

4.2.1 Efficacy Endpoints

Primary Efficacy Endpoint and Evaluation:

- Global assessment of spasticity (Modified Ashworth scale)

Secondary Efficacy Endpoints and Evaluations:

- Patient´s Quality of Life (QOL) evaluation (DAS scale)

- Interval between separate administration sessions

4.2.2 Safety Endpoints

Collection of treatment related adverse events.

4.3 Justification of Design

The aim of the Study is to provide additional risk / benefit information on the use of Dysport within the specifications of the SmPC. The Study 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 indication. As such, no additional measures of efficacy or safety are being collected other than those recorded in normal practice.

4.3.1 Study Duration

"Recruitment" period will be 18 months.

Duration of Study is approximately one year per subject (according to SmPC, 3 injections are expected within 1 year)

The Study will be considered to have started at first subject inclusion. It will be considered to have finished after the last visit(V5) performed by telephone contact.

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

5.1 Compliance with Good Clinical Practice and Ethical Considerations

This Study must be conducted in compliance with GCP, the Declaration of Helsinki and International Conference on Harmonisation (ICH)*, the Ipsen Ethical code, the Ethical Code of AIFP** and will be submitted to database of non-interventional studies in the SÚKL***. The Study will be submitted to Multicenter Ethical Committee.

In addition, this Study will adhere to all local regulatory requirements.

5.2 Informed Consent

Subject will be asked to sign simple informed consent.

Prior to study entry, the Investigator, or a person designated by the Investigator, will explain the nature, purpose of participation in this non-interventional study to each subject, subject's legally acceptable representative or impartial witness. Written informed consent must be obtained prior to the subject entering the study (before initiation of any study-related procedure and administration of the study drug). Sufficient time will be allowed to discuss any questions raised by the subject.

The Sponsor will provide a sample informed consent form. The final version must contain all elements included in the sample form, in language readily understood by the subject. Each subject's original consent form, personally signed and dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion, will be retained by the Investigator. The Investigator will supply all enrolled subjects with a copy of their signed informed consent.

The consent form may need to be revised during the trial should important new information become available that may be relevant to the safety of the subject or as a result of protocol amendments. It is the Investigator's responsibility to ensure that all subjects subsequently entered into the study and those currently in the study sign the amended form. This is documented in the same way as previously described. Subjects who have completed the study should be informed of any new information that may impact on their welfare/wellbeing.

* International Conference on Harmonisation (ICH) E9 and Federal register Vol 63, No. 179 (September 1998)

** Association of Innovative Pharmaceutical Industry (Asociace inovativního farmaceutického průmyslu)

*** State Institute for Drug Control (Státní Ústav pro Kontrolu Léčiv)

6. STUDY POPULATION

6.1 Subject Identification Code List and Number of Subjects

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

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

It is planned to recruit approximately 200 subjects in approximately 10-30 centres in Czech Republic.

6.2 Inclusion Criteria

All subjects must fulfil the following:

1) Subjects with stroke of either haemorrhagical or ischemic origin scheduled to receive Dysport, with stroke onset at least 3 months prior to study entry
2) Adults over the age of 18 years
3) Arm spasticity with Modified Ashworth scale ≥ 2 at least in one part

6.3 Exclusion Criteria

Subjects will not be included in the Study if :

1) Subject has hypersensitivity to Dysport (any of its components) or drugs with a similar chemical structure.
2) Subject is pregnant. Absence of pregnancy should be confirmed prior injecting the product.
3) Subject has been previously treated with any botulinum toxin.

6.4 Discontinuation /Withdrawal Procedures

Discontinuation of withdrawal should be recorded including the reason, if known

7. METHODOLOGY

7.1 STUDY Schedule

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

Table 1. Schedule of Observations

	V1 (D1)	**V2 (approx. D28)**	**V 3**	**V 4**	**V5 - phone contact approx 3-5 weeks after V4**
Demography& Eligibility	X				
Significant medical or surgical history	X				
Prior and concomitant medications	X				
Previous medication for stroke	X				
Treatment injections	X		X	X	
Related Adverse events	X	X	X	X	X
Modified Asworth assessment	X	X	Optional	Optional	X
DAS assessment	X	X	Optional	Optional	X
Interval assessment			X	X	

7.2 Study Visits

7.2.1 Baseline (Day 1, visit V1)

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

- Centre number, Subject number, Subject initials
- Demography
- Significant medical or surgical history
- Prior and concomitant medication
- Previous medication for stroke
- Stroke details
- Modified Ashworth scale, DAS scale
- Dysport administration (location, dosage)
- Related Adverse Events (at this visit injection related AEs only)

7.2.2 Follow-up visits (V2, V3, V4,V5)

At the subject´s scheduled return to the center (Visit 2, the date depends on investigator´s judgement, it is usually about 4 weeks later), the investigator will make routine control of treatment efficacy (V2). During this visit, both Modified Ashworth and DAS scales are evaluated according to routine practice. Treating physician will also perform an assessment of safety, and details on any treatment related adverse events will be collected.

After fadeaway of Dysport effect, subject will come to next injection visits (V3, V4,) within which Dysport will be injected again according to investigator decision. Treatment interval will be counted (V3 - V1, V4 - V3).

Visit V5 will be performed by telephone contact and is also the End of study visit.

During visit 5, which will take place within 3-5 weeks following last injection, subjects will be contacted by telephone to discuss any treatment related Adverse events (RAEs) that they have had since their treatment and Modified Asworth and DAS scale.

Collection of treatment related adverse events, if any, will be made during V1, V2,V3, V4 and V5.

7.2.3 Study Completion or Withdrawal

Study is completed if current visits exceed 1 year from visit 1 or when the Dysport treatment is finished/withdrawn

8. STUDY EVALUATIONS

For the timing of efficacy and quality of life assessments during the study, refer to the study schedule in section 7.1 and 7.2.

8.1 Efficacy Endpoints and Evaluations

8.1.1 Primary Efficacy Endpoint and Evaluations

- Global assessment of spasticity – Modified Ashworth scale will be used for efficacy evaluation.

8.1.2 Secondary Efficacy Endpoints and Evaluations

- Patient´s Quality of Life (QOL) evaluation – standard DAS scale will be used for QOL evaluation. Based on the subject interview, the investigator will fulfil the DAS QOL questionnaire, due to the absence of translated Czech version of the DAS.

- Interval between separate administration sessions – interval between current and previous injection visit will be described.

8.2 Safety Endpoints and Evaluations

8.2.1 Related Adverse Events

Treatment related AEs will be collected from the first treatment administration to the end of the Study. RAEs will be elicited by spontaneous reports. Due to the non-interventional character of the study, no pro-active safety data collection should take place and only spontaneously mentioned safety events should be reported. Further details for RAE reporting can be found in Section 10.

9. STUDY TREATMENTS

9.1 Study Treatments Administered

Administration of Dysport will be supervised by the Investigator.

Study medication

Chemical name:	*Clostridium botulinum* type A toxin-hemagglutinin complex
Study Code:	Dysport
Dosage form:	Inj. sicc.
Strength:	500 units / vial
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 solution for injection without preservative.

9.2 Subject Identification and Allocation to Study Treatment

All subjects enrolled must be identifiable throughout the Study. The Investigator will maintain a list of subject numbers and names at the Study center to enable records to be found at a later date if required.

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

9.3 Study Treatment Supply

The centre will prescribe Dysport, each bearing a unique batch number, by their normal method. The Dysport is the commercially available medicine in the Czech Republic.

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

9.4 Compliance

N/A

9.5 Study Treatment Storage

Until dispensed to the subjects, Dysport will be stored refrigerated under storage conditions mentioned in SmPC, as is the custom at the hospital/practice.

9.6 Concomitant Medication/Therapy

N/A

10. RELATED ADVERSE EVENT REPORTING

Only related to survey medication AEs will be registered during this survey.
An RAE 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, 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 RAE 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 Study.

10.1 Categorisation of Related Adverse Events

10.1.1 Intensity Classification

RAEs 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 subject
Severe:	symptoms definitely hazardous to well-being, significant impairment of function or incapacitation.

10.1.2 Causality Classification

Only those adverse events considered to be related to product will be collected.

RAEs are 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.

10.1.3 Assessment of expectedness

The expectedness of an RAE/reaction shall be determined by the Sponsor according to the Investigator's Brochure for an unapproved Survey medication or Summary of Product Characteristics (SmPC) or Package Insert for an authorised medicinal product which is being used according to the terms and conditions of the marketing authorisation. .
The reference document for assessing expectedness of RAEs/reactions in this survey will be: Summary of Product Characteristics, Czech Republic , Last approved version dated 30.06.2008, ref.nr.6324/2007;24731/2008;35386/2008).

10.1.4 Laboratory Test Abnormalities

NA

10.1.5 Abnormal Physical Examination Findings

NA

10.1.6 Other Investigation Abnormal Findings

NA

10.2 Recording and Follow-up of related adverse events

At each visit the subject 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 AEs related to survey medication will be recorded on the RAE page(s) of the CRF. Related 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.
RAEs already recorded and designated as 'continuing' should be reviewed at each subsequent assessment.
For all registered RAEs, the Investigator must pursue and obtain information adequate both to determine the outcome of the RAE and to assess whether it meets the criteria for classification as a RSAE requiring immediate notification to the Sponsor or its designated representative. The Investigator is required to assess causality and record that assessment on the CRF. Follow-up of the RAE, after the date of therapy discontinuation, is required if the RAE or its sequel persist. Follow-up is required until the event or its sequel resolve or stabilise at a level acceptable to the Investigator and the Sponsor's clinical monitor or his/her designated representative.

10.3 Related Serious adverse events

10.3.1 Definitions

All related to survey medication SAEs (as defined below) 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 Spontaneous report form.
A Related SAE is any RAE occurring at any dose that:

1. results in death;
2. is life threatening, that is any event that places the subject 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 subject 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 subject 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 related AE that the Sponsor or an Investigator considers serious should be immediately reported to the Sponsor and included in the corporate related 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 RAE (i.e., not associated with the development of a new RAE or worsening of a pre-existing condition) may meet criteria for "seriousness" but is not an adverse experience and thus is not subject 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 related SAE unless there are complications or squeal which meet the criteria for seriousness described above.

10.3.2 Reporting Requirments

In this Post Marketing Survey the collection of adverse events should be limited to related serious and related non-serious events . All related serious and related non serious adverse events will be reported by Investigator to Sponsor on the Spontaneus Adverse Event Report Form . Serious Adverse Events will be reported immediately (within 24 hours) by the investigator to the sponsor using the Spontaneus Adverse Reporting Form .

10.3.3 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 related SAE:

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

The additional information included in the related 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 RAE considered as the foremost untoward medical occurrence from secondary RAEs which occurred as complications.

10.4 Pregnancy

NA

10.5 Deaths

All related 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 related SAE within 24 hours of the Investigator’s knowledge of the event.
The convention for recording death is as follows:

- RAE 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 RAE term may be ‘Death’ or ‘Sudden death’.

10.6 Discontinuation/Withdrawal due to related adverse events/ related serious adverse events

Discontinuation/withdrawal due to RAEs 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 related SAE it must be reported immediately to the Sponsor's designated representative (see Section 10.3.3).
In all cases the Investigator must ensure the subject receives appropriate medical follow-up.

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

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 Study medication

11.2 Analyses Populations Definitions

- **ITT/Safety population:** All subjects who received at least one dose of Study medication

11.2.1 Populations Analysed

The analyses of efficacy and safety data will be performed based on the ITT/Safety population.

11.3 Sample Size Determination

This is a Post Marketing Study with a number of subjects where sample size of 200 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 (efficacy/safety and tolerability) Study, no statistical testing will be carried out.

11.4 Statistical/Analytical Methods

Statistical analyses will be performed / managed by CRO.

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.

11.4.1 Demographic and Other Baseline Characteristics

Descriptive summary statistics (n, mean, standard deviation (SD), median, minimum, maximum) of demographic and treatment dosage/interval will be presented.

11.4.2 Subject Disposition and Withdrawals

The numbers of subjects who were treated, discontinued and completed at each of the Study periods will be tabulated. Primary reasons for discontinuation of Study treatment will be tabulated.

11.4.3 Pharmacokinetic Data

N/A

11.4.4 Efficacy Evaluation

Descriptive analyses will be provided using Modified Ashworth scale and DAS scale at each visit and describing also changes from visit 1.

11.4.5 Safety Evaluation

All safety data will be included in the subject data listings. Analyses and summary tables will be based upon the safety population.
RAEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and will be classified by MedDRA preferred term and system organ class. RAE listings will be presented by subject, system organ class and preferred term.
Incidence of all reported RAEs/treatment emergent related AEs (TERAE) and SRAEs will be tabulated. In addition, summary tables will be presented by maximum intensity, drug relationship and RAEs/TERAEs associated with premature withdrawal of survey medication.
A TERAE is defined as any RAE 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 RAEs will be flagged (*) in the RAEs 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

N/A

11.6 Interim Analyses and Data Monitoring

N/A

11.7 Final Analysis

N/A

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. STUDY 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 Study documents and site facilities as specified in section 12.1, and to any other locations used for the purpose of the Study 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 Study 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 Study.

The Investigator must record all data relating to protocol procedures, Study medication administration, safety data and on the CRFs provided for the Study. 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 Study/ 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 Study 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 Study, the identity of the Study, the date that informed consent was obtained prior to participation in the study, diagnosis and eligibility criteria, visit dates (with subject status), Study medication administration, and spontaneously reported AEs and associated concomitant medication.

Definition for source data and source documents are given below:

- **Source Data:** All original records and certified copies of original records of clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). [ICH GCP Section 1.51]
- **Source Documents:** Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). [ICH GCP Section 1.52]

The items recorded directly on the CRF and considered as source data will be described at each site in a site specific document signed by the investigator and filed in the investigator file.

The subject must have consented to their medical records being viewed by Sponsor-authorised personnel, and by local, and possibly foreign, CAs. This information is included in the informed consent.

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 monitor/representative, directed by the Sponsor's Global Medical Affair 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 CRO 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 CRO , and reviewed and approved by the Sponsor. Concomitant medications will be coded using WHODRUG and AEs/medical history terms will be coded using MedDRA.

13.6 Study Management Committees

N/A

13.7 Record Archiving and Retention

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed.

Trial documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of clinical development of the product. However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the

Sponsor. The Investigator should take measures to prevent accidental or premature destruction of these documents. The final archiving arrangements will be confirmed by the monitor when closing-out the site. The Sponsor will inform the Investigator, in writing, as to when these documents no longer need to be retained.

If the Principal Investigator relocates or retires, or otherwise withdraws his/her responsibility for maintenance and retention of study documents, the Sponsor must be notified (preferably in writing) so that adequate provision can be made for their future maintenance and retention.

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 Study 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 Study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgement of the Sponsor.

The results of this Study may be published or communicated to scientific meetings by the Investigators involved in the Study. For multicentre Studys, a plan for scientific publication and presentation of the results may be agreed and implemented by the Study Investigators. 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 Study.

14.3 Clinical Study Report

A final clinical Study report will be prepared according to the ICH guideline on structure and contents of clinical Study reports, regardless of whether the Study 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 Study agreement prior to the start of the Study, outlining overall Sponsor and Investigator responsibilities in relation to the Study. The planned financial remuneration for investigator is 4 500,- CZK per completed CRF.

14.5 Insurance, Indemnity and Compensation

N/A

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 Study 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.

16. LIST OF APPENDICES

17. REFERENCES

Brashear A. et al: Inter- and intrarater reliability of the Modified Ashworth Scale and the Disability Assessment Scale in patients with upper-limb poststroke spasticity. Arch Phys Med Rehabil. 2002 Oct;83(10):1349-54.

Ashworth B: Preliminary trial of carisoprodal in multiple sclerosis. . Practitioner, 1964, 192: 540-2

Masur H: Symptomorientierte Skalen und Scores. Paresen. In: Skalen und Scores in der Neurologie. Quantifizierung neurologischer Defizite in Forschung und Praxis. 2nd ed. Stuttgart: Georg Thieme Verlag; 2000 p. 68-69

Modified Ashworth scale on affected upper limb – test on muscle spasticity

1) ELBOW FLEXORS	
No increase in muscle tone	☐ 0
Slight increase in muscle tone giving a "catch" when the limb was moved in flexion or extension	☐ 1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)	☐ 1+
More marked increase in muscle tone through most of the ROM , but limb was easily flexed	☐ 2
Considerable increase in muscle tone – passive movements difficult	☐ 3
Limb rigid in flexion or extension	☐ 4
2) FOREARM PRONATORS	
No increase in muscle tone	☐ 0
Slight increase in muscle tone giving a "catch" when the limb was moved in flexion or extension	☐ 1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)	☐ 1+
More marked increase in muscle tone through most of the ROM, but limb was easily flexed	☐ 2
Considerable increase in muscle tone – passive movements difficult	☐ 3
Limb rigid in flexion or extension	☐ 4

3) WRIST FLEXORS	
No increase in muscle tone	☐ 0
Slight increase in muscle tone giving a "catch" when the limb was moved in flexion or extension	☐ 1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)	☐ 1+
More marked increase in muscle tone through most of the ROM, but limb was easily flexed	☐ 2
Considerable increase in muscle tone – passive movements difficult	☐ 3
Limb rigid in flexion or extension	☐ 4
4) FINGER FLEXORS	
No increase in muscle tone	☐ 0
Slight increase in muscle tone giving a "catch" when the limb was moved in flexion or extension	☐ 1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)	☐ 1+
More marked increase in muscle tone through most of the ROM, but limb was easily flexed	☐ 2
Considerable increase in muscle tone – passive movements difficult	☐ 3
Limb rigid in flexion or extension	☐ 4
5) THUMB FLEXORS	
No increase in muscle tone	☐ 0
Slight increase in muscle tone giving a "catch" when the limb was moved in flexion or extension	☐ 1
Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the range of movement (ROM)	☐ 1+
More marked increase in muscle tone through most of the ROM, but limb was easily flexed	☐ 2
Considerable increase in muscle tone – passive movements difficult	☐ 3
Limb rigid in flexion or extension	☐ 4

Disability Assessment Scale (DAS) – test on Quality of Life (QOL)

1) LIMB POSITION: abnormal position of the upper limb	
No disability	☐ 0
Mild disability (noticeable but does not interfere significantly with normal activities)	☐ 1
Moderate disability (normal activities require increased effort and/or assistance)	☐ 2
Severe disability (normal activity limited)	☐ 3
2) HYGIENE: maceration, ulceration, and/or palmar infection; palm and hand cleanliness; ease of cleanliness; ease of nail trimming;+ and degree of interference caused by hygiene-related disability in the patient´s daily life	

No disability	☐ 0
Mild disability (noticeable but does not interfere significantly with normal activities)	☐ 1
Moderate disability (normal activities require increased effort and/or assistance)	☐ 2
Severe disability (normal activity limited)	☐ 3
3) DRESSING: difficulty or ease with which the patient can put on clothing (e.g. shiorts, jackets, gloves) and the degree of interference caused by dressing-related disability in the patient´s daily life	
No disability	☐ 0
Mild disability (noticeable but does not interfere significantly with normal activities)	☐ 1
Moderate disability (normal activities require increased effort and/or assistance)	☐ 2
Severe disability (normal activity limited)	☐ 3
4) PAIN: intensity of pain or discomfort related to upper limb spasticity	
No disability	☐ 0
Mild disability (noticeable but does not interfere significantly with normal activities)	☐ 1
Moderate disability (normal activities require increased effort and/or assistance)	☐ 2
Severe disability (normal activity limited)	☐ 3