HYPRO OTROKOVICE s.r.o.
Přístavní 568, 765 02 Otrokovice

CLINICAL STUDY OF THE MEDICAL DEVICE HYPRO-SORB® IN THE CLINICAL VARIANTS:

HYPRO-SORB R
HYPRO-SORB O
HYPRO-SORB NT
HYPRO-SORB Z
HYPRO-SORB F
HYPRO-SORB M

FINAL REPORT

(1)

Basic data

1. Study site:
Kroměřížská nemocnice a.s., (Kroměříž Hospital), Havlíčkova 660, Kroměříž 767 55, Czech Rep.
Business Registration Number (IČO): 24660532, Tax Registration Number (DIČ): CZ27660532

2. Clinical study title:
Clinical study of the product Hypro-Sorb® in its clinical variants R, O, NT, Z, F, M

3. Study product (variants):
Hypro-Sorb R®
Hypro-Sorb O®
Hypro-Sorb NT®
Hypro-Sorb Z®
Hypro-Sorb F®
Hypro-Sorb M®

4. Brief description of the clinical study:
The study products included the clinical variants R, O, NT, Z, F, M of the product Hypro-Sorb® in the form of dressing for dermatovenerology, plastic surgery, dentistry, treatment of burns as well as everyday medical practice. The study products, manufactured by HYPRO Otrokovice. s.r.o. in Otrokovice, Czech Republic, are intended for use by hospitals and other medical facilities. The evaluation was based on available publications, technical documentation provided, and reports of approved testing laboratories.

Owing to their properties (materials included, safety aspects) the study products comply with the stringent requirements for use by medical facilities.

5. Sponsor:
Antonín Galatík, Birth No. 7306174117, Komárov 69 763 61, Czech Republic

6. Manufacturer:
HYPRO Otrokovice s r.o., Přístavní 568, 76502 Otrokovice

7. Investigator:
MUDr. Lumír Domes, Karla Čapka 1785, Kroměříž 76701
Birth No.: 521102263

8. Sponsor's assistant:
None contracted.

9. Parts of the clinical study:
A. Study of available literature describing the study products, i.e. medical devices manufactured by Hypro Otrokovice, s.r.o.
B. Familiarization with the study products, application of published findings to the use and testing of their properties and performance, assessment with emphasis on the suitability of the study products for the intended purpose, their usefulness in routine practice, and non-existence of any health hazard arising from the use of the products in dermatovenerology, plastic surgery, dentistry, treatment of burns and routine medical practice.

10. Date of start of the clinical study: **15 September 2009**

11. Date of early termination of the clinical study: **Not applicable**

12. Date of finish of the clinical study: **22 October 2009**

13. Date of issue of this final report: **5 November 2009**

Contents of this final report

This final report describing clinical evaluation of the Hypro-Sorb® dressing product in its clinical variants R, 0, NT, Z, F, M for dermatovenerology, plastic surgery, dentistry, treatment of burns and routine medical practice comprises 17 pages including annexes.

List of abbreviations, glossary of terms

None

Qualifications of the investigator, MUDr. Lumír Domes

Date of birth:	2 November 1952
Home address:	Karla Čapka 1758, 76701 Kroměříž, Czech republic
Office:	Kroměříž Hospital, Havlíčkova 660, 76701 Kroměříž
Position:	Head of Department of Urology
Education:	1959-1972 Grammar School
	1972-1978 Faculty of Medicine in Volgograd, Russia
	1978-1983 Certification of Urology I
	1983-1988 Certification of Urology II.
	1992- Head of Department of Urology
Experience:	30 years
Short-term attachments:	Germany, Sweden, France
Participation in studies:	1992-1996 participation in EORTC trials

00-OMN-01 A randomised, double-blind, placebo-controlled, parallel group, dose-response study of tamsulosin oral controlled absorption system (OCAS) 0.4 mg, 0.8 mg and 1.2 mg tablets once daily in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO), formerly known as symptomatic benign prostatic hyperplasia (BPH).

02-0MN-02 A randomised, double-blind, placebo-controlled study to evaluate efficacy and safety of tamsulosin oral controlled absorption system (TOCAS) 0.4 mg, 0.8 mg and 1.2 mg tablets once daily, tamsulosin modified release 0,4 mg capsules (OMNIC) once daily and placebo in patients with lower urinary tract symptoms (LUTS) suggestive of benign prostatic obstruction (BPO), formerly referred to as symptomatic benign prostatic hyperplasia (BPH).

A309904 Open randomised study of previously untreated metastatic prostate cancer patients comparing intermittent to continuous treatment with cyproterone acetate. Evaluation of step-up therapy adding an LHRH agonist progression is included. 905-EC-001 Solifenacin in flexible dose regimes with tolterodine as an active comparator in a double-blind, double-dummy, randomised overactive bladder symptom trial.

20050103 A randomized, double-blind, multicenter study of denosumab compared with zoledronic acid (Zometa) in the treatment of bone metastases in men with hormone-refractory prostate cancer.

Other persons participating in the clinical study

None

Information regarding the testing of the study products for the intended use

1. Objectives and justification:

- Assessment of the study product with respect to its safety to the user and to third persons when providing medical care within the scope specified in the product documentation / catalogue.
- Assessment of the study product's suitability for the intended use and agreement with current clinical knowledge.
- Assessment of the study product's suitability for medical care provision within the scope specified in the product documentation / catalogue.
- Assessment of the study product's suitability for use in the Czech Republic.

2. Related legislation:

- Act No. 130/2003 amending Act No. 123/2000 on medical devices and on the amendment of some related acts, and some other acts.
- Governmental Decree No. 180/1998 laying down technical requirements for medical devices, as amended by Governmental Decree No. 130/1999.
- Act No. 22/1997 on technical requirements for products, as amended by Act No. 71/2000 and Act No. 205/2002.
- Decree of the Ministry of Health No. 316/2000 laying down details regarding the contents and structure of clinical study reports.

3. Clinical study plan

Assessment of the suitability of the use of study products by medical facilities for patient care and treatment, based on available publications, technical documentation and investigator's own knowledge and experience, with emphasis on the products' suitability, safety, and any side effects and risks associated with their use.

The investigator will be provided with following items by the sponsor:

- Clinical assessments by 3 medical facilities
- Risk management documentation based on EN ISO 14971, EN 12442 and Annex XII to Governmental Decree No. 336/2004
- Declaration of conformity
- A specimen in the original packaging plus information leaflet
- A report of *in vitro* cytotoxicity testing and skin tolerance testing dated 18 December 2008

Clinical information will be extracted from documentation and publications available at the time of the study.

The investigator will study the publications, assess the performance and quality of the various study products, and assess the suitability of their use by medical facilities. The investigator will develop a document describing clinical assessment of the study product, Hypro-Sorb®, in the clinical variants R, O, NT, Z, F, M for dermatovenerology, plastic surgery, dentistry, treatment of burns, as well as routine medical practice, and will provide the document to the sponsor, Hypro Otrokovice s.r.o. in Otrokovice.

The sponsor will immediately prepare a final clinical study report and submit it to the management of the Kroměříž Hospital (Kroměřížská nemocnice a.s.) and its Ethics Committee for approval.

Clinical assessments of the study products

Atelocollagen is collagen freed from telopeptides which contain interspecies antigenic determinants, whereby the tissue tolerance is increased. Collagen, especially Type I, activates a cascade of interactive steps in the blood fluid, consisting of activation of zymogen to the enzyme thrombin, which in turn induces proteolysis of fibrinogen giving rise to a soft granulation clot which is then transformed to hard granulation matter. Type I, II and III collagens and their degradation products have been shown to act as chemotactic stimulators of fibroblasts *in vivo* and to efficiently help repair damaged tissue.

Atelocollagen, the basis of Hypro-Sorb, is manufactured from bovine heel tendons taken from animals intended for human consumption and individually inspected by veterinaries. Since no alternative tissue source exists for the manufacture of atelocollagen, which is the most efficient known hemostatic featuring outstanding tolerability by human tissues, resorbability, non-immunogenicity and promotion of the skin lesion healing process, no material other than one of animal origin can be used. The use of skin as a source of atelocollagen is inappropriate because skin contains Type I and III collagen, elastin, and also the motor protein myosin, which is a source of antigens. Although theoretically possible, the use of raw material other than of animal origin is associated with enhanced risks, such as immune reaction to a very different collagen, whereby the product safety would be impaired. The use of bovine collagen in the manufacture of resorbable hemostatics has the longest history and is best documented. The animal breeding process is subject to stringent regulations and veterinary inspections, and moreover, sufficient domestic sources are available, owing to which a high level safety of the material can be ensured.

Common properties of the study products

Mechanism of action:

Hemostasis is a heterogeneous process occurring at the interface of collagen (solid) - body fluid (blood, wound exudate). The kinetics of the heterogeneous processes is primarily dependent on the interface area, hence, on the internal surface area of the dressing. The internal surface area of Hypro-Sorb exceeds 150,000 cm^2/cm^2, which is one of the highest known values among hemostatics. The time of hemostasis is 3 to 5 minutes in physiologically normal patients and 5 to 10 minutes in hemophiliacs and heparinized patients.

The mechanism of action is based on the natural specific activity of collagen, resulting in release of coagulation factors, which in combination with blood plasma factors forms the sealing fibrin substance which stops bleeding. In addition, collagen inhibits exudate serine proteinases and promotes granulation and epithelization of chronic wounds and wounds which do not heal smoothly.

Implanted Hypro-Sorb is absorbed by the tissue within 3 to 4 weeks (in dependence on its amount and on the site on the body). The mechanism of absorption and biotransformation is based on the action of specific enzymes – latent collagenases – which are activated in the tissues during injuries and healing. Collagenases are also present in hepatocytes, itoic cells, lysosomes, granulocytes and other cell structures near the wound. Preclinical tests have shown that the process is apyrogenic (without inflammatory reaction) and the presence of macrophages (inflammation cells) is irrelevant to the resorption of Hypro-Sorb. The absorption process results in slow hydrolysis of the collagen protein to give soluble peptides and aminoacids, which are metabolised by the tissue cells during the synthesis of the ligament. This is why it is tolerated by human tissues without any immune reaction and is metabolised through a mechanism similar to that of the tissue's own collagen.

Packing

The study product is packed in a combined packaging consisting of paper and internal packaging comprising a PET blister and outer polyethylene (PE) packaging. The packaged products are sterilized by gamma irradiation (outsourced process). The packaging contains chemical indicator marking of sterilization process validation. The packaging displays the following bilingual (Czech and English) information:

- Product name
- Size in mm
- Number of pieces in a packaging
- Product composition
- Information about the presence of a user information leaflet
- Manufacturer
- International batch number identification, catalogue number, date of manufacture, expiry date, sterilization data, identification of a single-use product, notified body identification
- Bar code

The packaging is fault-free, aesthetically satisfactory, no defects that might compromise sterility were detected on the packaging of the specimens submitted. The packaging is easy to store and does not occupy too much space, which is an important factor in hospitals. A wide choice of sizes is available, and so the user can select from various variants as the need may arise.

The packaging is easy to handle, comfortable to open, the product can be easily removed from the packaging without any hazard of compromising sterility as might be associated with a packaging that is difficult to open. The study products are free of defects, workmanship quality is outstanding.

Risk analysis

1. Incoming material selection risk
2. Risk of contamination by bacteria, moulds or yeasts
3. Risk of contamination by viruses or infectious agents, prions, BSE
   - Animals
   - Origin
   - Nature of the starting material
   - Methods used to inactivate or remove any infectious agents
   - Amount of starting animal material needed to manufacture one unit of the study product
   - Amount of material of animal origin coming in contact with patients and users
   - Method of application
4. Control of origin, extraction and handling
   - Identification of the geographical origin, i.e. country where the cattle was bred, health status of the animal and acceptability criteria
   - Requirements for hygiene and quality assurance of the slaughtering procedure
   - Procedures of extraction, conservation, handling, storage, and transport of the tendons
   - Records kept
   - Inspection and control
     a. Procedures
     b. Personnel
     c. Conformity with current requirements
     d. Origin of the animal material
     e. Check of the source of the animal material, origin certification and traceability
     f. Occurrence of spongiform encephalophathies
     g. Documentation of the breeding and feeding procedures and history
     h. Method of animal stunning
     i. Extraction and handling
     j. Validation of the elimination and/or inactivation of viruses and infectious agents
     k. General rules for elimination of any source of BSE
     l. Continuous monitoring and control of the decisive parameters of elimination
     m. Review of the assessment

The documentation appended clearly demonstrates that the issues of a safe extraction of the material, validation and inspection / control are well managed by the manufacturer. All aspects of good manufacturing practice are elaborated in detail with a view to minimizing any conceivable side effects of the study product. The documentation thoroughly describes all potential risks associated with the use of the study product along with appropriate risk assessments. In general, risks associated with the origin of the material, its processing, manufacture and use when adhering to all application rules as described in the user information leaflet are minimal to negligible.

Product name and type

Hypro-Sorb® R, absorbable atelocollagen hemostatic felt, sterile, available in the following sizes:

Product number	Name	Size
001	Hypro-Sorb R	65x110 mm
002	Hypro-Sorb R	65x55 mm, 2 pieces
003	Hypro-Sorb R	20x25 mm, 6 pieces
006	Hypro-Sorb R	10x10x10 mm, 10 pieces
012	Hypro-Sorb R	65x55 mm

Product composition

The product consists of pure (99.9%) crystalline bovine Type I atelocollagen, native and absorbable, in the form of nonwoven felt.

Indications:

- To stop capillary and parenchymatous bleeding in surgery, traumatology and dental surgery, especially where routine procedures are insufficient or difficult to perform.
- Dressing for bleeding superficial wounds and abrasions
- Dressing for sites from which skin implants have been taken
- Cover of burns

Contraindications:

- Hypro-Sorb should not be used to stop spurting arterial bleeding.
- Hypro-Sorb should not be inserted into bone fractures bonded with acrylonitrile adhesives because it reduces the bonding strength.

Use

Removed from the sterile package, Hypro-Sorb R should be directly applied to the bleeding surface and compressed slightly. The time of application depends on the type and extent of bleeding, type of surgery and preoperative patient preparation. Bleeding will stop typically in 2 to 5 minutes. Hypro-Sorb R is most efficient when dry but it can be pre-moistened with saline to facilitate shaping. Hypro-Sorb R can be left in the incision: it has a reduced antigenic determinant content and is very welll tolerated in the incision.

Hypro-Sorb® O, absorbable atelocollagen hemostatic felt, sterile, triangular shape

Product number	Name	Size
007	Hypro-Sorb O	5x15 mm, 20 pieces

Product composition

The product is pure (99.9%) crystalline bovine Type I atelocollagen, native and absorbable, sterile, in the form of nonwoven felt, shape of a triangle 5 mm base and 15 mm height.

Indication:

- To dry the operative field in ophthalmology a neurosurgery

Contraindications:

- None

Use

Removed from the sterile packaging, the Hypro-Sorb O triangle is directly applied to area to be dried or to the bleeding surface. The major asset of atelocollagen when used in order to dry wounds is in its excellent hemostatic effect when stopping capillary bleeding, owing to which it provides both for good drying and for efficient hemostasis during surgery. Hypro-Sorb O is most efficient when dry but it can be pre-moistened with saline to facilitate shaping. Hypro-Sorb O can be left in the incision: it has a reduced antigenic determinant content and is very well tolerated in the incision.

Hypro-Sorb® Z, absorbable atelocollagen hemostatic insert shaped as a tooth root, sterile

Product number	**Name**	**Size**
009	Hypro-Sorb Z	Tooth insert, 10 pieces

Product composition

The product is pure (99.9%) crystalline bovine Type I atelocollagen, native and absorbable, sterile, in the form of nonwoven felt shaped as a tooth insert with anatomical modelling.

Indications:

- To stop bleeding following tooth extraction or other surgery in the mouth cavity.
- To stop bleeding in predisposed persons with natively or pharmacologically reduced blood coagulation.

Contraindications:

- None

Use

Removed from the sterile packaging, the Hypro-Sorb Z inserts shaped as tooth roots are directly applied in the mouth cavity. Periodontal diseases and caries are among the most widespread lifestyle diseases. Sometimes, gingival or subgingival bleeding is an accompanying effect. In addition, many dental disorders are treated by surgery, where stopping bleeding may pose a problem.

Remedy is rather simple in patients with normal blood coagulation and taking no anticoagulants. However, if the patient suffers from hemophilia or if his or her blood coagulation is reduced by drugs, situations threatening the patient through massive blood loss can arise. Increased bleeding is also a side effect of long-acting anaesthetics such as bupivacaine and etidocaine. Their vasodilative effect brings about problems of massive bleeding, especially during surgeries associated with the removal of considerable amounts of soft or bone tissue. In addition, the emerging residual postoperative cavities can be sources of postoperative bleeding from the remaining tissue. Collagen hemostatics are efficient in inducing local hemostasis in children suffering from hemorrhagic diathesis. This method is much safer and less costly than the use of blood products in substitution therapy, and is especially well suited for children with Type A hemophilia with factor VIII antibodies. Hypro-Sorb R can be left in the incision: it has a reduced antigenic determinant content and is very well tolerated in the incision.

Hypro-Sorb® NT, absorbable atelocollagen hemostatic sponge, sterile

Product number	Name	Size
008	Hypro-Sorb NT	10x30 mm, 5 pieces

Product composition

The product consists of pure (99.9%) crystalline bovine Type I atelocollagen, native and absorbable, in the form of a sponge of nonwoven felt.

Indication:

- To stop nosebleeding, especially from the middle or back part of the nasal cavity.

Use

Removed from the sterile packaging, the Hypro-Sorb NT sponges are inserted into the nostril with an end protruding in order to facilitate removal when bleeding is over. By pressing slightly on the side of the nose the sponge is compressed to get in intimate contact with the bleeding mucosa, in 2 to 5 minutes the sponge is removed applied directly to the bleeding surface and compressed slightly. The time of application depends on the type and extent of bleeding, type of surgery and preoperative patient preparation. Hypro-Sorb NT is most efficient when dry but it can be pre-moistened with saline to facilitate shaping. Hypro-Sorb NT can be left in the incision: it has a reduced antigenic determinant content and is very well tolerated in the incision.

Hypro-Sorb® F, absorbable atelocollagen hemostatic monolayer or bilayer barrier, sterile, available in the following sizes:

Product number	Name		Size
020	Hypro-Sorb F	monolayer barrier	15x20 mm
021	Hypro-Sorb F	monolayer barrier	20x30 mm
022	Hypro-Sorb F	monolayer barrier	30x40 mm
023	Hypro-Sorb F	bilayer barrier	15x20 mm
024	Hypro-Sorb F	bilayer barrier	20x30 mm
025	Hypro-Sorb F	bilayer barrier	30x40 mm

Product composition

The product consists of pure (99.9%) crystalline bovine Type I atelocollagen, free from telopeptides, native and absorbable, apyrogenic.

Indications:

- In jaw surgery and implantology or in the reconstruction of bone defects by GTR/GBR
- Cystectomy
- Segmental alveolar bone growth
- Maxillary sinus elevation
- Root apex resection
- Alveola filling following extraction in preprosthetic surgical practice
- Periimplants
- Plastics of the oroantral system

Guided tissue regeneration (GTR) has become the basic therapeutic procedure of choice in the treatment of peridontal bone defects, as well as bone defects of periimplantitis and during augmentation procedures prior to the placing of implants. (In such cases the technique is referred to as guided bone regeneration (GBR)). Research has shown that barriers (membranes) are capable of preventing the ingrowth of epithelization cells or fibroblasts into the bone defect, thus making for bone reconstruction by normal bone tissue growth. This concept has been applied to the treatment of parodontal defects with the aim of reconstruction of cement, peridontal connection and bone.
Very thin (0.05 mm) monolayer barriers are maily used where the barrier need not be fixed.
Bilayer barriers provide outstanding Type I collagen matrices for bone integration on their rough porous side, as well as for adhesion and healing of soft tissue on their smooth side.

Contraindications:

- Hypro-Sorb F should not be inserted into bone fractures bonded with acrylonitrile adhesives because it reduces the bonding strength.

Use

Hypro-Sorb F is trimmed to the desired size with scissors. The barrier should overreach the defect edges by a minimum of 2 to 3 mm in order to achieve complete bone coverage and prevent lateral ingrowth of the gingival tissue. The defect cavity is then filled with a bone substitute material such as Ossaplast. Hypro-Sorb® F is applied to the defect with its smooth side up and held in place with moderate pressure. Soaked with blood and exudate, the barrier can be perfectly adapted to the bone surface. Stabilization with pins may be used for complex defects. The flaps are sutured over the barrier tightly but without tension (e.g. using the single sutures or mattress suture). If possible, the wound should be closed completely. Any stress or palpation in the wound area should be avoided during the healing phase. Intensive mechanical oral hygiene should be replaced by antibacterial rinsing during the first 3 weeks. Antibiotic therapy can be prescribed at the clinician's discretion.

Hypro-Sorb® M, bioabsorbable biphase matrix for guided tissue/bone regeneration, sterile, available in the following sizes:

Product number	**Name**		**Size**
030	Hypro-Sorb M	biphasic barrier	16x20 mm
031	Hypro-Sorb M	biphasic barrier	22x32 mm
032	Hypro-Sorb M	biphasic barrier	32x42 mm

Product composition

The product consists of pure (99.9%) crystalline bovine Type I atelocollagen, free from telopeptides, native and absorbable, apyrogenic.

Indications:

- In jaw surgery and implantology or in the reconstruction of bone defects by GTR/GBR
- Cystectomy
- Segmental alveolar bone growth
- Maxillary sinus elevation
- Root apex resection
- Alveola filling following extraction in preprosthetic surgical practice
- Periimplants

- Furcation treatment
- Cleft lip, cleft palate

Hypro-Sorb® M has a specific activity to thrombocytes and induces release of clotting factors, which together with plasma binding factors promote fibrinogenesis. Other tissue interactions include inhibition of collagenolytic activity of the wound exudate, support of granulation, epithelisation, promotion of the soft tissue healing process and GTR/GBR.

Contraindications:

- Hypro-Sorb M should not be inserted into bone fractures bonded with acrylonitrile adhesives because it reduces the bonding strength.

Use

Hypro-Sorb M is trimmed to the desired size with scissors. The barrier should overreach the defect edges by a minimum of 2 to 3 mm in order to achieve complete bone coverage and prevent lateral ingrowth of the gingival tissue. The defect cavity is then filled with a bone substitute material such as Ossaplast. Hypro-Sorb® M is applied to the defect with its smooth side up and held in place with moderate pressure. Soaked with blood and exudate, the barrier can be perfectly adapted to the bone surface. Stabilization with pins may be used for complex defects. The flaps are sutured over the barrier tightly but without tension (e.g. using the single suture or mattress suture). If possible, the wound should be closed completely. Any stress or palpation in the wound area should be avoided during the healing phase. Intensive mechanical oral hygiene should be replaced by antibacterial rinsing during the first 3 weeks. Antibiotic therapy can be prescribed at the clinician's discretion.

Conclusions

The following conclusions can be drawn from the study and evaluation of the existing preclinical, clinical and comparative investigations:

1. Hypro-Sorb R is the most efficacious known product to stop capillary bleeding.
2. Hypro-Sorb activates a cascade of coagulation factors in blood in a natural manner.
3. The material features a high absorbing capacity: 1 g of the sponge absorbs as much as 100 g of a fluid.
4. It does not tear or stick to surgical instruments or gloves when wet.
5. It is implantable, fully bioabsorbable and apyrogenic.
6. Inhibiting serine proteinases it has a slightly bacteriostatic effect.
7. Hypro-Sorb does not support microorganism growth, owing to which it can be applied to infected wounds, e.g. in medically compromised patients.
8. In tests aimed at comparing Hypro-Sorb with the medical devices HEMOPAD and SUWELACK, Hypro-Sorb was superior to the two other products in all clinical parameters examined.
9. The study product meets all qualitative requirements for products intended for the medical sector. It has long been used in clinical practice, the material as well as the manufacturing procedures complies with recommended standards, as demonstrated by certificates and the detailed risk analysis document.
10. The study product is a product of simple nature, and when used for the intended purposes and in agreement with the instructions for use, it does not pose a health hazard or hazard of damage to the patient.
11. In our experience, the study product is fully comparable with analogous medical devices used in the medical sector.

Concluding statement

The medical device Hypro-Sorb® in its clinical variants R, O, NT, Z, F, M, manufactured by HYPRO OTROKOVICE s.r.o., which was subject to clinical assessment, is recommended for use in clinical practice and complies with requirements for use by third parties.

(2)

Annexes

a) Ethics Committee's written consent to the implementation of the clinical study.
b) Ethics Committee's statement regarding compliance of the clinical study performed with ethical principles.
c) References
d) Supplements:
- Request for consent to the implementation of a clinical study of a medical device
- Contract between the sponsor and the investigator and the study site.
- Investigator's statement

(Signatures, stamps:)

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Kroměřížská nemocnice a.s.
Represented
by
Ing. Pavel Calábek,
Chairman of the Board of
Directors

….....
MUDr.Lumír Domes
Investigator

….....
Hypro Otrokovice s r. o.
represented
by
Antonín Galatík,
company secretary

Otrokovice, 5 November 2009