



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Bonn, Germany, 19 July 2012
EMA/482305/2012
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report for SecreFlo

International non-proprietary name: secretin human

Procedure no. EMEA/H/C/2027

Applicant: Repligen Europe Limited

This Withdrawal Public Assessment Report is based on the CHMP Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.
This should be read in conjugation with the "Question and Answer" document on withdrawal of the application.



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LIST OF ABBREVIATIONS

AGA: American Gastroenterological Association
AUC: Area Under the Curve
CHMP: Committee of Human Medicinal Products
CL: Corpora Lutea
C_{max}: Maximum Concentration
CPMP: Committee for Proprietary Medicinal Products
CT: Computed Tomography
CU: Clinical Unit
EC: European Community
EMA: European Medicines Agency
EP: European Pharmacopoeia
ERA: Environmental Risk Assessment
ERCP: Endoscopic retrograde cholangiopancreatography
EU: European Union
EUS: Endoscopic ultrasound
GLP: Good Laboratory Practices
ICH: International Conference on Harmonisation of Technical Requirements for
Registration of Pharmaceutical for Human Use
IADB: Indiana University Database
i.v.: Intravenous
Kg.: Kilogram
mg: Milligram
microg: Microgram
min.: Minute
ml: Millilitre
MRCP: Magnetic Resonance Cholangiopancreatography
MRI: Magnetic Resonance Imaging
MTD: Maximum Tolerated Dose
NOAEL: No Observed Adverse Effect Level
NOEL: No-observed Effect Level
OECD: Organization for Economic Co-operation and Development
Ph.Eur.: European Pharmacopoeia
PK: Pharmacokinetic
RG1068: SecreFlo
RIA: Radioimmunoassay
s.c.: Subcutaneous(ly)
SmPC: Summary of Product Characteristics
S-MRCP: Secretin-enhanced MRCP
SWP: Safety Working Party
T_{max}: Time of occurrence of C_{max}
USA: United States of America
USP/NF: United States Pharmacopoeia/National Formulary

1. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for SecreFlo "for use with magnetic resonance imaging (MRI) to improve pancreatic duct visualization for the detection of duct abnormalities to enhance clinical decision making in adults with known or suspected pancreatitis." **is not approvable** since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- The single pivotal trial is a post-hoc analysis (i.e. re-reading of images) of the unreliable original phase III trial. Re-reading of images is not acceptable unless the company assures and fully documents that bias avoidance measures related to new readers blinding and training were fulfilled.
- Subjects in the pivotal trial are not representative of the population in whom this diagnostic agent is intended to be used.
- Data on clinical efficacy of RG1068-enhanced magnetic resonance cholangiopancreatography (MRCP) from the single pivotal study are very limited. See also "other concerns". The results of sensitivity and specificity have unclear clinical relevance, and are affected both by the flawed cluster-based method to calculate them and by the standard chosen for the final diagnosis of the recruited patients which was non-standardised and non-justified as appropriate.

Questions to be posed to additional experts

N/A

Inspection issues

GMP inspection(s)

N/A

GCP inspection(s)

Given that there is only a single pivotal trial for this application, which is indeed a post-hoc analysis (i.e. re-reading of images) of the original phase III trial that the company itself considers unreliable, some bias avoidance measures should be assured for re-reading to be considered acceptable.

2. EXECUTIVE SUMMARY

2.1. Problem statement

Acute pancreatitis is a serious condition which refers to inflammation of the pancreas. The incidence of acute pancreatitis varies considerably throughout the world. Recent data suggest that the incidence is comparatively low in England and the Netherlands (perhaps 5–10 per 100,000), is somewhat higher in Scotland and Denmark (approximately 25–35 per 100,000 inhabitants), and is still higher in the United States and Finland (approximately 70–80 per 100,000 inhabitants). The incidence appears to be increasing, but this data may reflect improved methodology of diagnosis and more accurate record keeping. (Banks 2002).

A multicenter prospective study of patients with acute pancreatitis reported overall mortality of 5 percent (Banks et al. 2006). Advances in diagnostic and therapeutic interventions have led to a decrease in mortality from acute pancreatitis, especially in those with severe pancreatitis.

There is general acceptance that a diagnosis of acute pancreatitis requires two of the following three features: 1) abdominal pain characteristic of acute pancreatitis, 2) serum amylase and/or lipase ≥ 3 times the upper limit of normal, and 3) characteristic findings of acute pancreatitis on CT scan (Banks et al. 2006). Once a diagnosis of acute pancreatitis is made, additional tests are needed to determine the underlying cause.

A number of conditions are known to induce this disorder: mechanical ampullary obstruction induced by gallstones and a variety of disorders (stenosis, cancer, diverticulum, etc.), toxics (alcohol...), metabolic causes (hypertriglyceridemia, hypercalcemia), genetic mutations, many drugs with different potential for causing acute pancreatitis, infections, trauma, pancreas divisum, vascular disease and miscellaneous (post-ERCP, pregnancy, celiac disease, autoimmune and anorexia nervosa). In up to 75% of cases, acute pancreatitis is due to gallbladder stones or alcoholism.

Imaging the pancreas using computed tomography (CT) and magnetic resonance imaging (MRI) has utility describing changes of the pancreatic parenchyma and peri-pancreatic spaces. In situ, the duct anatomy is small, variable and has little inherent contrast in tissue density or water content from its surrounding structures. The technical difficulties imaging the pancreatic ducts has resulted in endoscopic retrograde cholangiopancreatography (ERCP) having a diagnostic role. ERCP involves the cannulation and direct injection of radio-opaque dye into the main and accessory pancreatic ducts with imaging with fluoroscopy. ERCP is associated with significant morbidity and mortality. Complications due to ERCP (acute pancreatitis, duct perforation, hemorrhage and infection) limit its diagnostic use to those indications for which it may offer definitive treatment.

Magnetic resonance cholangiopancreatography (MRCP) was introduced in 1991 to image the biliary and pancreatic ducts using thick slab, T2-weighted acquisition parameters in which the entire collection system is captured in a single rapidly accessed image. MRCP provides accurate depiction and measurements of the bile and pancreatic ducts in 95 percent of examinations; associated anatomic variants, such as pancreas divisum and choledochal cysts, and pancreatic ductal disruptions can also be visualized. The technique is useful for documenting communication between pancreatic cysts and ducts, and for evaluating the nature of pancreatic cysts. However, since it is fluid within ducts that is depicted, MRCP cannot differentiate between focal strictures and spasm of the common bile duct.

The guidelines by the American Gastroenterological Association (AGA) issued an approach to determining the etiology of acute pancreatitis (Forsmark et al. 2007) based on history, serum levels of some parameters, an abdominal ultrasound. Only in some particular cases, extensive or invasive evaluation is recommended depending on the patient's age, the suspected etiology.... This extensive or invasive evaluation is recommended by means of different techniques (endoscopic ultrasound (EUS), CT, ERCP, MRCP) depending on the clinical context.

References:

- Banks PA. Epidemiology, Natural History, and Predictors of Disease Outcome in Acute and Chronic Pancreatitis. In: NIH State-of-the-Science Conference on Endoscopic Retrograde Cholangiopancreatography (ERCP) for Diagnosis and Therapy. 2002
- Banks PA, Freeman ML, F.A.C.G. and the Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. Am J Gastroenterol 2006;101:2379–2400.

- Forsmark CE, Baillie J, AGA Institute Clinical Practice and Economics Committee, AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. *Gastroenterology* 2007; 132:2022.

2.2. About the product

RG1068 was developed for use with MRCP for the detection of pancreatic duct abnormalities. Prior to developing RG1068 for S-MRCP, RG1068 was used in clinical studies for autism and schizophrenia and obsessive-compulsive disorder.

It is identical in sequence to human secretin, a gastrointestinal peptide hormone that is produced by S-cells in the duodenum. Secretin is released in response to the pH decrease caused by the passage of partially digested food from the stomach into the intestine. Secretin stimulates the secretion of a bicarbonate-rich fluid by the pancreas, which neutralizes the acidified duodenum. Secretin also inhibits the production of gastrin in the stomach and potentiates the stimulation of pancreatic enzyme secretion by cholecystokinin.

Secretin-stimulated MRCP exploits the action of secretin to enlarge the pancreatic ducts with fluid to improve the resolution of MRCP by increasing the size and the T2-weighted signal within the pancreatic duct system. Furthermore, it is a dynamic study in which the physiologic response to secretin and the outflow of pancreatic juice through the ducts into the duodenum provide valuable functional information of the pancreatic ducts.

Other secretin products were or are currently approved in Europe and USA. Their primary use has been the assessment of pancreatic exocrine function. Those still marketed in USA (ChiRhoStim, a human synthetic product) and in Europe (Secrelux, a porcine synthetic product), are both approved for exocrine pancreatic function testing and for detection of gastrinoma, and ChiRhoStim also to facilitate the identification of the ampulla of Vater during endoscopic retrograde cholangiopancreatography (ERCP). None is authorized for enhanced MRCP, although they are both used "off-label" (to our data) in Europe and in USA for this purpose. According to a metaanalysis provided in this submission, previously or currently marketed secretin products have been used for this requested indication.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program for human secretin was done under consideration of the CHMP Guideline for Clinical Evaluation of Diagnostic Agents (CPMP/EWP/1119/98/Rev. 1) and the points to consider for submitting a single pivotal study in support of marketing authorization should be followed (CPMP/EMA/2330/99). They were not fully fulfilled (see related comments on discussion of efficacy).

Scientific Advice regarding the clinical development was provided by CHMP: four advices for the indication of MCRP and 1 for diagnosis of Zollinger-Ellison Syndrome.

The clinical development of the product hardly adhered to the given advices.

In summary, the proposed cluster-based methodology to calculate the primary endpoints (i.e. sensitivity and specificity for unenhanced MRCP and enhanced-MRCP) in the phase III study was found to be systematically biased, having a potential undesirable effect on statistical testing and conclusions. CHMP previously advised the company to choose another method for evaluation of sensitivity and specificity which involves unbiased estimators. For this, it was highly recommended to express test performance in a binary measure on a per-patient level, reflecting the need to show a benefit in clinical decision making. It was also advised to the company to use a "less complicated, more readily interpretable and more clinically relevant measures". In connection to this,

demonstration of an improved negative predictive value for the enhanced MRCP over unenhanced MRCP was considered an important element when it comes to discuss the diagnostic advantages of the enhanced method.

The Company has submitted re-reading of the phase III study, and not the original study, as the confirmatory study to evidence efficacy in this application. Despite former scientific advices given, this re-reading consisted of a retrospective analysis of the phase III study images but without changing the flawed cluster-based methodology to calculate the primary endpoints and flawed study design of the original study. Additional demonstration of improved negative predictive value of enhanced-MRCP versus unenhanced MRCP is still missing.

No studies in special risk populations were conducted.

No paediatric development has been performed. The PDCO agreed on a paediatric investigation plan and on the granting of a deferral for RG1068. The plan covers the entire pediatric age range from birth to less than 18 years of age with suspected pancreatic disease (inflammatory, infectious, congenital anomalies, trauma) for a similar indication as in adults.

2.4. Type of application and other comments on the submitted dossier

- Legal basis

This application concerns a centralised procedure (according to Regulation (EC) No 726/2004).

This is a complete application in accordance with article 8(3) of Directive 2001/83/EC as amended, for approval of a new active substance through the centralised procedure with ES acting as Rapporteur and UK as Co-Rapporteur. The application concerns SecreFlo, which contains the active substance secretin human. This application is also under evaluation by FDA.

- Accelerated procedure

N/A

- Conditional approval

There is currently no application for conditional or for approval under exceptional circumstances. At the initiation of the phase III study, the company asked the CHMP if meeting criteria for Conditional Marketing Authorization for RG1068 to be used in stimulated MRCP in patients with acute (recurrent) pancreatitis. The CHMP recommended to go for full approval after the phase III study since the requirements for a conditional marketing authorisation was not met: the product did not address an unmet medical need and the positive benefit-risk balance could not be concluded with the results from the phase II clinical study.

- Exceptional circumstances

N/A

- Biosimilar application

N/A

- 1 year data exclusivity

N/A

- Significance of paediatric studies

No paediatric development has been performed. The waiver request was withdrawn by the applicant. The PDCO agreed on a paediatric investigation plan and on the granting of a deferral for RG1068. The plan covers the entire pediatric age range from birth to less than 18 years of age with suspected pancreatic disease (inflammatory, infectious, congenital anomalies, trauma) for a similar indication as in adults.

3. SCIENTIFIC OVERVIEW AND DISCUSSION

3.1. Introduction

SecreFlo (also known as RG1068) is a secretin intended for use in MRCP for imaging the pancreatic duct in adults with known or suspected pancreatitis.

The following indication is proposed by the applicant:

"SecreFlo injection is indicated for use with magnetic resonance imaging (MRI) to improve pancreatic duct visualization for the detection of duct abnormalities to enhance clinical decision making in adults with known or suspected pancreatitis."

The proposed posology to be administered is 25 micrograms (if weighing 50 kg or greater) or 0.2 micrograms/kg body weight (if weighing less than 50 kg) as a single intravenous injection over 30 seconds followed by a 10 ml normal saline flush over 30 seconds.

3.2. Quality aspects

Active substance

Secretin is a 27 amino acid synthetic, C-terminal amidated peptide.

With reference to the definition of New Active Substance as provided in Annex III of NtA Vol 2A Chapter 1, the Applicant should provide data to support that secretin is a NAS in itself - i.e. not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorised substance - or if the properties with regard to the safety and efficacy of secretin against the authorised active substance are significantly different.

Synthesis, purification, release testing, packaging, labeling and stability testing of the active substance are currently performed by the manufacturer at its Belgian site. Tests used for the release of the active substance may also be performed by several subcontractors.

General information on active substance is sufficient. However, the applicant uses different names for the active substance in the documentation: "secretin", "secretin human", "synthetic human secretin" or "secretin, synthetic human". According to the ASMF, the INN name of the active substance is "secretin". A clarification of this discrepancy is requested.

Description of manufacturing process and process controls is, in general terms, adequate.

The validation program performed by the manufacturer for the active substance consisted of the manufacture of three consecutive campaigns yielding three lots of the active substance according to cGMP at a scale equivalent to the initial commercial scale. Since the active substance is not manufactured by a sterile or aseptic process, this is considered sufficient.

Manufacturing process development along different campaigns is adequately described. Only minor changes on the manufacturing process have been performed and quality of active substance is sufficiently maintained along time.

Elucidation of Structure is performed by adequate tests. All the studies have been performed with a batch obtained according to the current manufacturing process. Information is sufficient.

Description of formation and fate of potential and real impurities is, in general terms, adequate. However, a discussion on potential genotoxic impurities is not provided and this has been requested.

The specification, proposed limits and analytical methods are generally satisfactory but some clarifications have been requested. Specifications from the manufacturer responsible for batch release of the product do not include several of the active substance manufacturer's specifications. A justification is requested. The expression of assay is on an "as is" basis, rather than on the anhydrous, acetic acid free substance, which is not considered satisfactory. Routine control of enantiomeric purity has also been requested. Some proposed limits are requested to be narrowed according to Ph. Eur. or the batch data presented.

Analytical procedures employed by release testing manufacturer are described and validated. Some of them are the same as the ones used in finished product testing, and other were not originally validated by the finished product release site but were transferred to it. Original validation and method transference reports have been included.

The proposed container closure system are amber glass bottles (Type III, Ph. Eur./USP) closed by a polypropylene auto-sealing cap. However, bottles sizes range from 5 ml to 2500 ml, and taking into account the small quantities of active substance obtained in the synthesis process, this point is not justified. Bottle sizes should be stated according to batch size, or justified.

In general terms, stability studies are adequate. However, the capacity of the bottles employed in the stability studies is requested, together with a discussion on influence of headspace on water content of the active substance. Additionally, taking into account that the re-test period for active substances intended for storage in a freezer should be based on the real time data obtained at the long term storage condition, update of stability data from validation batches has been requested.

Finished product

SecreFlo finished product is a lyophilized cake containing 25.0 µg peptide, and mannitol, sodium citrate and Polysorbate 80 as excipients. Prior to use, each vial is reconstituted with 5.0 mL of Normal Saline, USP. It is packaged in single-use 10 ml, type I USP glass vials with 20 mm stoppers. The vial is sealed with a 20 mm, royal blue, flip-off seal. The diluent is not packaged with the RG1068 finished product.

Composition of the product is well described, with reference to the standards and percentage of each compound in the table. The company identified the physico-chemical properties of the active substance that are clinically relevant for the patient. These properties have been adequately specified and they are adequately controlled. Since the formulation is prepared as a solution, the key physicochemical characteristic of API affecting finished product is solubility. All excipients used to manufacture RG1068 finished product are USP/NF or Ph.Eur. quality.

Formulation development for RG1068 finished product was designed around the challenges of handling extremely small amounts of peptide per vial. The applicant states that "the manufacturing process has been developed to achieve RG1068 content of 90-110%." However, Directive 75/318/EEC as amended states "unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished products shall not exceed $\pm 5\%$ at the time of manufacture". Moreover, the possibility that there are substances arising from the loss of active substance which may not be captured by the purity methods should be explored.

A study about compliance of the reconstituted vial to Ph. Eur. monograph 2.9.17 Test for extractable volume of parenteral preparations (ICH Topic Q4B Annex 2) should be carried out, in order to control the withdrawability of the product.

RG1068 finished product is manufactured and packaged by the finished product manufacturer for Repligen Corp. A manufacturer's flow chart has been included. The three steps of the manufacturing process are well defined: bulk formulation, sterile filtration/fill and lyophilization. Taking into account that active substance degrades after exposure to high heat, sterile filtration is considered adequate as sterilization method. Some studies about the use of filters demonstrate that there are no losses of the active substance when passing through the filters. Filter validation studies were also performed. Filter compatibility, extractables, bacterial challenge and bubble point were examined.

Description of manufacturing process (sterilisation by filtration followed by lyophilisation) and process controls is provided. Flow diagram with indication of the critical steps is submitted. The holding times have been properly justified. The manufacturing method has been validated using three full-scale production batches which have been processed in the same manufacturing facilities, using the same process and the same equipment as for the batches intended for marketing. All process validation reports have been annexed in the dossier, including experimental data for all of them. However a major objection concerns sterility assurance of the product as there is no control on bioburden before sterile filtration. The assurance of sterility is based on all the steps taken during the manufacturing process to reduce the bioburden presented to the sterilising filters since end-stage sterility is not a reliable means of ensuring that every unit manufactured is sterile. Also, the maximum value of bioburden seen to date (2 cfu per 10ml or 20 cfu per 100ml) is higher than the maximum 10 cfu per 100ml recommended in the Note for Guidance on Manufacture of the Finished Dosage Form - CPMP/QWP/486/95. Routine control of bioburden to appropriate limits and an improvement of the manufacturing process will be required.

It is also not clear what are the responsibilities of each of the participants in the manufacturing and control processes, since for the validation tables, it seems to be that final product is only analysed by the product release site and not the manufacturer, and the only analytical certificates of validation batches provided are from Repligen (applicant). In addition, partial analytical certificates of the three validation batches from the manufacturer are provided (particulate matter, endotoxins and sterility), but the validation results of the same parameters in the validation batches from Repligen do not coincide with the manufacturer's results for the same batches, and it is indicated that those analytical results have been not reviewed by the manufacturer. In conclusion, a clarification is needed about the real responsibilities of each of the participants in the control of the final product, together with description and validation of analytical methods used by each of the controllers.

Regarding the excipient water for injection, reference to Ph. Eur./USP is made. However, both references are not equivalent, because USP allows the use of reverse osmosis in the production of water for injection while Ph.Eur. does not. A clarification is requested; method of production of water for injection should be precised in order to confirm the reference to Ph. Eur.

The product specification is adequate for this type of formulation. Taking into account that the final product is a lyophilisate and the results of the batches tested, the specification for water content is considered too wide and should be narrowed. Specification for assay (release and shelf-life) should be narrowed to comply with Directive 75/318/EEC. The proposed test procedures and acceptance criteria follow the principles of the ICH Q6A guideline. Analytical methods were transferred from a previous analytical testing site to the current analytical testing site or their subcontractors with the corresponding method numbers. The overall approach to the method transfer is summarized in a protocol with specific transfer reports for general methods such as appearance, pH, reconstitution time, water content and particulates as well as the microbiological tests of endotoxin and sterility. The HPLC methods were partially re-validated. However, there are a number of concerns relating to control of impurities.

Taking into account that chapter <71> of USP has undergone pharmacopoeial harmonisation with chapter 2.6.1 of Ph. Eur., this test can be accepted to control the sterility of the product. The same occurs with chapter <85> of USP and 2.6.14 of Ph. Eur. in relation to control of quantitation of endotoxins by

bacterial endotoxins chromogenic technique. And it also occurs with chapter <905> of USP and 2.9.40 of Ph. Eur., in relation to control of uniformity of dosage units.

Analytical certificates of batches RCM-11-0003, RCM-11-004 and RCM-11-0006 are not valid, since specification for assay is 80-125 %, different and much wider than that applied in the specifications table. In addition, manufacture place and batch size (volume of formulated bulk and number of units filled) of these batches are unknown. There are also concerns about an impurity found in one of the developmental batches which is considered to be a manufacturing contaminant. It has been stated that this impurity is excluded by improvements in the manufacturing process but further assurance is required.

The quality profile of all reference materials has been correctly established.

A description of the container closure systems has been provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications include description, identification and critical dimensions. The containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life. A statement of compliance of packaging materials with European Pharmacopoeia Monograph has been provided.

The stability studies have been carried out only on primary stability batches in accordance with current ICH/CHMP guidelines. The analyses were carried out in accordance with the relevant analytical procedure, using validated stability-specific methods. Assay and water content specifications at shelf-life are not acceptable.

There are important deficiencies in the stability section of the dossier: the batches selected for stability studies (manufactured by process 2A and 2B) cannot be considered representative of the commercial process (process 3) and therefore the assessment of the stability section of the dossier is not possible. According to ICH Q1A, data should be provided from batches manufactured according to the manufacturing process in section 3.2.P.3.3.

In addition, the same active substance batch was used to manufacture all batches. According to ICH Q1A, where possible, batches of the finished product should be manufactured by using different batches of the active substance. Therefore, stability should be evaluated using different batches of the active substance, otherwise justified.

As per NfG on Stability Testing: Stability Testing of New Active substances and Products (CPMP/ICH/2736/99), and taking into account the nature and characteristics of the final product (it is a non-standard product), a minimum of 12 months covered by data at submission should be included at long-term conditions, and 6 months at accelerated conditions.

Discussion and Conclusions on chemical, pharmaceutical and biological aspects

Two major objections and several points to clarification have been raised and they need to be solved to guarantee the quality of the product.

3.3. Non clinical aspects

Pharmacology

Secreflo™, also referred to as RG1068, 25 micrograms, powder for solution (for injection), is a synthetic peptide comprised of 27 amino acids. It is identical to naturally-occurring human secretin, a gastrointestinal peptide hormone that is normally released from the intestinal enterochromaffin cells upon exposure of the proximal lumen of the duodenum to acidic content from the stomach (Bayliss and Starling, 1902). Secretin binds to secretin receptors on pancreatic duct cells in response to the pH decrease caused by the passage of partially digested food, chyme, from the stomach into the intestine

(Jin et al, 1994) and it stimulates the secretion of pancreatic juice, a bicarbonate rich fluid which acts to neutralize the acidity of the chyme (Diamond and Siegel, 1940; Jorpes and Mutt, 1966).

SecreFlo™ is being developed for use with magnetic resonance imaging (MRI) to improve pancreatic duct visualization for the detection of duct abnormalities to enhance clinical decision making in patients with known or suspected pancreatitis. This method of detection, also named magnetic resonance cholangiopancreatography (MRCP), is the preferred methodology for pancreatic imaging because it is radiation-free (Darge and Anupindi, 2009), less expensive and less invasive than other methodologies. MRCP uses the fluid content of the biliary and pancreatic ducts to visualize the pancreaticobiliary system on T2-weighted images (Takehara, 1996). However, MRCP alone has limitations of resolution and degree of visualization for the duct structures (Arvanitakis et al, 2004), since the duct anatomy is small, variable and has little inherent contrast in tissue density. RG1068-enhanced MRCP improves the visualization of the pancreatic ducts and the surrounding tissue by promoting the secretion of pancreatic juice, which acts as an intrinsic contrast medium.

There are only two amino acid differences in the primary sequence of porcine and human secretin and, across species, secretin is highly homologous. Rats and dogs have been selected as appropriate species to study intravenous dosing due to the conservation of endogenous secretin sequence between these species and human. Human secretin is identical to rat secretin in 24/27 amino acids and identical to dog secretin in 26/27 amino acids. Human secretin has been reported to bind rat secretin receptors (Shen et al., 1996) and porcine secretin, which is identical to dog secretin in 26/27 amino acids, has been shown to bind dog secretin receptor (Jin et al, 1994).

RG1068 has been characterized in the pancreatic provocation assay in cats (BP011 study). In the QT9900717 study, RG1068 was determined to have an activity of 0.19 microg/clinical units (CU) versus biological porcine secretin, and showed dose dependent increases in pancreatic secretion. The assessor would like to note that the report of QT9900717 has not been submitted like non-clinical documentation and it is included as part as quality information. Indeed, the Applicant has not provided a full evaluation of the pharmacology of RG1068. Hence, the Applicant should provide a revised non-overview that include a review of the published literature on the pharmacology of secretin and how it relates to RG1068.

Also the potential of RG1068 to adversely affect central nervous system (CNS) and cardiovascular function was evaluated by the Irwin test in rats (Irwin, 1968) and in repeat-dose of i.v. administered RG1068 in dogs and minipigs, respectively.

No pharmacodynamic drug interactions studies with RG1068 have been performed. This lack could be acceptable if it is considered that RG1068 is similar to human secretin.

Pharmacokinetics

The pharmacokinetics properties of the digestive hormone secretin have been studied in depth and are considered well known in several animal species and human, following different administration routes.

RG1068 is expected to have similar characteristics to the human secretin. Although RG1068 plasma pharmacokinetics has not been extensively characterized in preclinical or clinical studies, studies to determine RG1068 plasma pharmacokinetics have been conducted in rats and dogs (by i.v. administration) and in Göttingen minipigs (after i.v., s.c. and transcutaneous administration), using radioimmunoassays (RIA).

So, after i.v. administration of RG1068, the maximum average C_{max} and AUC values achieved were 4083 ng/mL and 26751 ng min/mL in rats, 445 ng/mL and 2743 ng min/mL in dogs and 8.6 ng/mL and 32.2 ng min/mL in minipigs, respectively. The plasma clearance values ranged from 31.96 mL/min/Kg to 256.78 mL/min/Kg in the rat, from 59.47 to 132.72 mL/min/Kg in dogs and from 122.3 mL/min/Kg to 124.1

mL/min/Kg in minipigs, while the terminal half-life values ranged from 2.3 to 19.1 min in the rat, from 1.2 to 8.9 min in the dog and from 2.42 mL/min/Kg to 6.1 min in minipigs.

Although no specific distribution studies were performed, the data calculated in different repeat-dose toxicology studies performed in rats and dogs indicated a distribution volume for RG1068 of 537 L/Kg and to 161.4 mL/Kg, respectively, after intravenous administration of the 0.4 microg/Kg dose. Such distribution volumes were substantially larger in the rat and dog compared to humans.

On other hand, RG1068 dosed s.c. at 0.044 mg/kg produced a similar C_{max}, 5.34 to 6.12 ng/mL, to that seen with 0.004 mg/kg i.v. while there is a 4-fold increase in AUC with s.c. injection. On the contrary, the transcutaneous injections achieved a C_{max} of secretin in plasma more rapidly than the i.v. injections.

The data of these studies show that the plasma secretin concentrations declined in a biexponential manner in rats and dogs following i.v. administration of RG1068. However, in minipigs dosed i.v., both the C_{max} and AUC were equivalent after the first and the last dose.

Toxicology

The toxicology of Secreflo™ have been studied both in single and repeat-dose toxicity studies in rats and dogs dosed i.v. with RG1068 and in and repeat-dose toxicity studies in minipigs dosed i.v., s.c. and transcutaneously.

The findings reported in the single dose toxicity studies were a scab in the neck in one female rat and the depressed and dark areas in the left pulmonary lobes of the male dog and were considered no related to treatment. The MTD was established higher than 1000 microg/kg/day for both studies.

The repeat-dose toxicity studies have been performed in rats and dogs after i.v. injection up to 28 days with doses ranging from 0.86 to 861 microg/kg in rats, and from 0.86 to 258 microg/kg in dogs, although the dogs were not administered daily if not every third day for the 28 days.

No deaths at any dose were reported in any toxicology studies.

In the non pivotal study performed in rats during 7 days, skin red slight in limbs and nose in one rat receiving 85.5 microg/kg were reported on day 3 and a slightly elevated LDH value in one female at 8.5 microg/kg/day dose group was also observed.

In other repeat-dose study also performed in rats, microscopic findings in the testes at dose levels of 861 microg/kg/day and in the ovaries as well as persistent CL at 25.8 and 861 microg/kg/day, and at 861 microg/kg/day in the recovery phase (2 weeks) were found. Also, slight redness of the forepaws, hind paws, pinnae and/or nose were other findings observed in few rats in all secretin-treated groups. The NOAEL for this study was established to 0.86 microg/kg/day.

In dogs, vacuolation of the germinal epithelium of the testes was found at all doses assayed and therefore, the NOAEL was also established to 0.86 microg/kg/day.

In RSZ012/042309 study performed in minipigs, a significantly increase of weight of testes of males administered with 4 microg/kg i.v. and 800 microg/kg transcutaneously was observed.

In these repeat-dose toxicity studies different vehicles were used for the test and control groups,

Although the Applicant has not submitted a toxicokinetics section, the Assessor filled it in taking into account the PK data. So, at the NOAEL dose, the exposure multiples in dogs was about 0.2-fold on day 13, but the exposure could not be determined on day 1 and day 25 because there was also insufficient plasma concentration. In same way, in rat, at NOAEL of 0.86 microg/kg, the exposure could not be also determined. In minipigs, the exposure multiple was 0.6-fold on weeks 1 and 4. Therefore, the safety

margin is low but, taking into account the expected single administration of RG1068 in humans, this is not a concern.

Genotoxicity and carcinogenicity studies have not been performed with RG1068. Also, no antigenicity, immunotoxicity and dependence studies have been carried out.

The effects of RG1068 only have been assayed in fertility and in juvenile animals. In a study performed in rats was noted a slight decrease in the fertility indices in female rats dosed at 40 microg/kg/day. In other hand, reddening of the ears, snout and eyes were observed in juvenile dogs dosed at 40 microg/kg/week.

No animals were dosed with RG1068 during the gestation period and during peri y postnatal development.

The local tolerance of RG1068 was tested with the Draize evaluation and no adverse reactions not expected with any intravenous and perivenous injection were reported. In this study sodium chloride 9 mg/mL (0.9%) was used as the control vehicle but it was not used to formulate the test article. Therefore the Applicant should explain why a different vehicle was used for the test article, and discuss the possible consequences of this for the interpretation of local tolerance of the final product.

Neither antigenicity and immunotoxicity studies as well as dependence and metabolites studies have been carried out.

No studies have been conducted on impurities, nor were these discussed in the Non-Clinical Overview.

Ecotoxicity/environmental risk assessment

Secreflo™ is a 27 amino acid peptide and, according to Article 8(3) of Directive 2001/83/EC and Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/4447/00 corr 1*), the ERA is not enforceable, as the Applicant has set out.

Besides, the Company has provided the Predicted Environmental Concentration (PEC) for surface water that is 1.25×10^{-4} .

The ERA Guidance states "If the $PEC_{SURFACEWATER}$ value is below 0.01 microg/L, and no other environmental concerns are apparent, it is assumed that the medicinal product is unlikely to represent a risk for the environment following its prescribed usage in patients."

Thus no environmental assessment report is required for Secreflo™: the active substance is like a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, the synthetic human secretin is not expected to pose a risk to the environment.

Discussion on non-clinical aspects

The cat pancreatic provocation assay submitted to assess the activity of RG1068, (BP011 study) is a bit confusing. The activity of RG1068 was determined in the QT9900717 study, included as part of quality documentation. Further, a full evaluation of the pharmacology of RG1068 has not been provided by the Applicant.

The safety pharmacology studies, although they were in compliance with GLP, were not conducted in accordance with the safety pharmacology core battery as defined in the ICH guidance S7A, as well as a GLP hERG assay to investigate effects on ventricular repolarisation and arrhythmias was not performed and the potential effects of RG1068 at respiratory system was not addressed. However ICH S7A guidance also indicates that safety pharmacology studies are not required for compounds with low systemic exposure or distribution. So, taking into account the indication of the product, the lack of these studies is not a concern.

Regarding the dose used in PK and toxicology studies, there are several discrepancies in the administered doses between the study reports and PK tabulated summary and the toxicology written summary.

On other hand, the Applicant should clarify why PK data have not been reported by gender, since males and females of every animal species have been used in the studies.

The Applicant considers the redness observed in several toxicity studies of limited toxicological significance since they are in a low frequency. However these findings should be considered treatment-related effects as they are reported in both rats and dogs. In the same way, the significantly increase of weight of testes of males administered with 4 microg/kg i.v. and 800 microg/kg transcutaneously observed in minipigs, could be treatment related, taking into account the findings found in the germinal epithelium of the testes both in rats and dogs.

As it is mentioned previously, ovarian and testicular findings were noted in a repeated dose toxicity study in rats dosed at 25.7 or 855 µg/kg RG1068 for 28 days. However, no such findings were observed in the single reproductive toxicity study conducted with up to 40 µg/kg RG11068. So, the applicant should comment on this difference.

The lack of genotoxicity, carcinogenicity, antigenicity, immunotoxicity, metabolites and dependence studies performed with RG1068 is acceptable and is justified according with the current European guidelines.

The effects of RG1068 only have been assayed in fertility in rats and in juvenile animals. In rats, the slight decrease in the fertility indices was not considered to be related to administration of the test article since these values are within historical control range for the laboratory. However, it was not rejected taking into account the toxicological findings found in testes and in ovarian in repeat-dose toxicity studies. So, the Applicant should clarify which are these controls and their scientific basis.

Also, in the study performed in juvenile dogs, the Applicant states that no effects on indices of reproductive maturity or competence were noted but, as RG1068 produces vacuolation of germinal epithelium of testes of dogs in repeat-dose toxicity studies, an effect of RG1068 on male reproduction can not be discarded. So this should be indicated in the summary of product characteristics (SmPC).

Since any animals were dosed with RG1068 during the gestation period and during peri y postnatal development, it is not know whether human synthetic secretin can cause fetal harm, affect to prenatal and postnatal development and the maternal function. This should be also indicated in the summary of product characteristics (SmPC). Also, the applicant should provide a justification for the omission of the standard pivotal reproductive and developmental studies using two species

The test used to assay the local tolerance of RG1068, the Draize evaluation, is controversial. The Applicant should have taking into account the Council Directive 2010/63/EU or an in vitro test could have been performed to address the irritative potential of RG1068. On other hand, the Applicant should explain why a different vehicles were used for the test and control groups and discuss the possible consequences of this for the interpretation of local tolerance of the final product.

Since studies have not been conducted on impurities, the Applicant should comment on the presence or absence of any impurities in the RG1068 formulation and their genotoxic potential. Any impurities that exceed the qualification threshold should be suitably qualified.

The assessors would like to point out that the order of presentation of information in the toxicological written summary should meet the requirements established by the guideline ICH M 4S, common technical document for the registration of pharmaceuticals for human use – Safety (CPMP/ICH/2887/99-Safety).

RG1068, the active substance is like a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, the synthetic human secretin is not expected to pose a risk to the environment.

Conclusion on non-clinical aspects

Overall, the provided primary pharmacodynamics study has not been explained the pharmacodynamics of RG1068 from a non clinical point of view. Hence, the Applicant should provide a revised non-overview that include a review of the published literature on the pharmacology of secretin and how it relates to RG1068.

Although the PK and toxicology of RG1068 can be considered acceptable, some issues have to be solved by the Applicant.

3.4. Clinical aspects

The company contends that the clinical utility of RG1068-enhanced MRCP has been demonstrated by the findings in two key studies (phase II RG1068-15 and phase III RG1068-16RR), supported by the retrospective database analysis of the Indiana University and a metaanalysis of the published literature. They do not consider the original RG1068-16 study as basis for this application with the argument that efficacy was inadequately assessed. To this regard, CHMP admitted that in the original study RG1068-16 overall the performance of the test personnel was below requirements and quality control has only been sloppily adhered to.

The company sought approval for RG1068-stimulated MRCP in patients with acute (recurrent) pancreatitis at the first advices. However, without changing the studied population in phase III trials, the company had already modified the intended population to be, not patients with acute (recurrent) pancreatitis as initially, but with pancreatitis in general.

Tabular overview of clinical studies

Table 2.7.3. Summary of Clinical Efficacy Studies Relevant to the Claimed Indication

Study ID	Number of study sites enrolling/ Location	Study start date/ Study completion date	Design and control type/ Development stage	Study and control drugs/ Dose, route and regimen/ Lot/batch #	Key study objective(s)	# Patients enrolled/ analyzable ^a / safety	Duration/ diagnosis/ gender M/F/ mean age	Key efficacy assessments
Key RG1068 Studies								
RG1068-16RR	23 sites USA, Canada	26 March 2008 28 October 2009	Assessor blinded, baseline control, MRCP imaging using ERCP as truth standard Phase III	RG1068 IV infusion; patients ≥ 50 kg received 22.5 μg ; patients weighing < 50 kg received 0.2 $\mu\text{g}/\text{kg}$ after a 4-hour fast Lot RCM-07-0001	Assessment of sensitivity and specificity of MRCP imaging with and without RG1068 stimulation; safety of RG1068 infusion	E:258 C:RG1068-MRCP: 258 ERCP: 254 Abnormalities by ERCP: 142 S:258 safety	Single dose Acute or acute recurrent pancreatitis scheduled for ERCP 93M/165F 47.7 years	Presence or absence of pancreatic duct abnormalities, image quality, reader confidence, duct visualization, ERCP prevention index
RG1068-15	15 sites USA	22 August 2006 05 January 2007	Assessor blinded, baseline control, MRCP imaging using ERCP as truth standard Phase II	RG1068 IV infusion; patients ≥ 50 kg received 18.5 μg ; patients < 50 kg received 0.2 $\mu\text{g}/\text{kg}$ after a 4-hour fast Lot RCM-01-0010	Assessment of sensitivity and specificity of MRCP imaging with and without RG1068 stimulation; safety of RG1068 infusion; PD	E:80 C:RG1068-MRCP: 80 ERCP: 77 Abnormalities by ERCP: 41 S:80 safety	Single dose Acute or acute recurrent pancreatitis scheduled for ERCP 24M/56F 45.5 years	Presence or absence of pancreatic duct abnormalities, duct visualization, image quality, reader confidence, pancreatic duct diameter



Study ID	Number of study sites enrolling/ Location	Study start date/ Study completion date	Design and control type/ Development stage	Study and control drugs/ Dose, route and regimen/ Lot/batch #	Key study objective(s)	# Patients enrolled/ analyzable ^a / safety	Duration/ diagnosis/ gender M/F/ mean age	Key efficacy assessments
Supportive Secretin								
Indiana University MRCP Database Study Report	1 site USA	January 2003 May 2005	Database analysis; prospectively defined assessment; blinded readers Control was two-fold; external truth standard (ERCP) and pre-dose/post-dose MRCP image assessment Analysis focused on patients with acute/acute recurrent pancreatitis	16 µg synthetic porcine secretin (SecreFlo™) Negative contrast agent - up to 300 mL of silicone-coated supramagnetic iron oxide oral (GastroMARK™) 30 minutes before the MRCP following a fast of at least 4 hours	Assessment of sensitivity and specificity of MRCP imaging with secretin stimulation; PD	110 evaluated 50 - acute or acute recurrent pancreatitis 48 - chronic acute abdominal pain (most with normal ERCP and MRCP) 12 - intraductal papillary mucinous neoplasm (IPMN) S:N/A	Single dose Unexplained acute and acute recurrent pancreatitis 32M/84F 47 years (median)	Presence or absence of pancreatic duct abnormalities, image quality, pancreatic duct diameter
Literature Meta-analysis	N/A	Literature from January 1994 to January 2011	Literature database search - use of secretin with MRCP Meta-analysis methodology used for analysis	Secretin (Secrelux, Sekretolin, Secrepan, SecreFlo, ChiRhoStim, other, unspecified) Median dose (range): 0.2 µg/kg (0.1-2.0 µg/kg); 1.0 CU/kg (0.5-4.0 CU/kg); IV; single dose	Comprehensive review assessing safety and efficacy of S-MRCP to improve structural delineation of pancreatobiliary structures; assess diagnostic sensitivity and specificity of S-MRCP	Efficacy: 18 articles including 1200 patients Safety: 76 articles including 3714 patients	571M/434F ^b Normal controls (n=7 articles); acute pancreatitis (n=6); chronic pancreatitis (n=5); suspected pancreatic disease (n=7); tumor (n=1); strictures/stenosis (n=1); other (n=5) Age range: 0.2 to 86 years	Number of main pancreatic duct segments identified, duct diameter, image quality, presence or absence of abnormalities

a Studies with ERCP truth standard

b Not all publications reported the male:female demographics; therefore, the number of males and females do not add to the total
Abbreviations: CU = clinical unit; ERCP = endoscopic retrograde cholangiopancreatography; IV = intravenous; MRCP = magnetic resonance cholangiopancreatography; PD = pharmacodynamics

Source: Tabular Listing of All Studies, Section 5.2; Clinical Study Reports, Section 5.3; Literature Review, Module

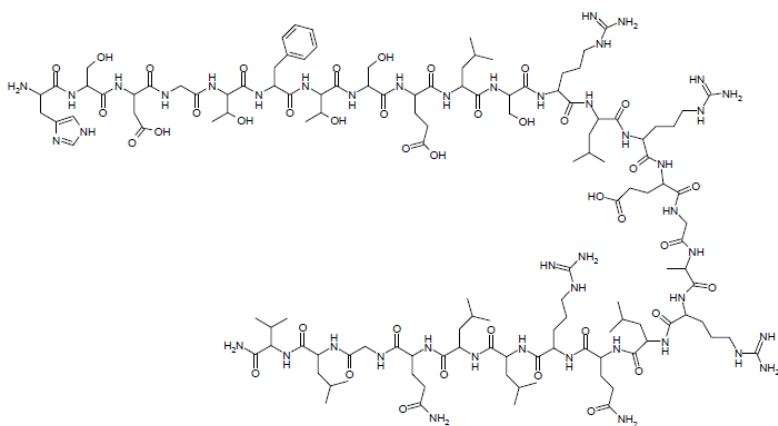
Pharmacokinetics

RG1068 (synthetic human secretin, Secreflo) is an intravenous formulation of a 3,039.5 Dalton synthetic 27 amino acid gastrointestinal peptide. RG1068 corresponds to a diagnostic agent developed for use with magnetic resonance imaging (MRI) to improve pancreatic duct visualization for the detection of duct abnormalities in order to enhance clinical decision making in patients with known or suspected pancreatitis.

Secreflo is available as a 10 ml vial that contains 25 micrograms of purified synthetic human secretin as lyophilized white to off white powder. After reconstitution with 5 ml sodium chloride (0.9%) solution for injection, each millilitre of solution contains 5 micrograms of secretin. The reconstituted solution has a PH of 6.0-7.5.

The molecular formula of Secreflo is C₁₃₀ H₂₂₀ N₄₄ O₄₀ and its chemical structure it is shown below.

Structure of RG1068 active substance



Analytical Methods

Plasma samples were analyzed using a commercial human secretin RIA kit (Bachem-Peninsula Laboratories S-2189.0001) in studies 05 and 09 under documented protocols SOP-5003-00 and FM-01-5003-00.

The competitive assay format involved incubation of secretin containing samples with a capture antibody in the presence of 125I labelled secretin competitor. Secretin levels were measured by comparing the signal generated by the sample and an externally generated calibration curve.

Briefly, all samples were run as duplicates in the RIA assay and compared against the external, matrix matched (80% pooled, human plasma) calibration curve for quantitative determinations. Many samples required dilution with 80% plasma in order to produce a result that fell within the quantifiable region of the calibration curve.

An assessment of blinded control samples from study 01 indicated low precision of the RIA assay used in this study.

PK studies

The pharmacokinetics (PK) of intravenous RG1068-05 was studied in three clinical studies; two studies performed in healthy adult males (RG1068-05 and RG1068-09) and one study performed in children with autism (RG1068-01) (see tabular listing below) Results from study RG1068-01 were not discussed due to the reliability issues with the assay.

RG1068-05 - Phase I randomized, double blind, placebo-controlled study to assess the pharmacokinetics and effects by functional MRI of one dose of RG1028 on Facial Affect Recognition in healthy normal volunteers. A total of 12 healthy male volunteers were enrolled and analysed. Six subjects received one dose of RG1028 2CU/kg IV (0.4 mcg/kg) and 6 subjects received one dose of placebo IV.

RG1068-09 - Phase I randomized, single-blind placebo-controlled study to assess the safety, tolerability and pharmacokinetics of RG1068 via subcutaneous injections and intravenous infusions in healthy normal volunteers. This was a dose-escalation, five-way crossover design conducted to compare the PK of RG1068 when administered via subcutaneous injection and intravenous infusion in healthy volunteers, and to determine the safety and local tolerability of subcutaneous administration. A total of 12 healthy male volunteers were enrolled and 9 subjects completed the clinical phase of the study.

RG1068-01- Phase I/II randomized, double blind, placebo controlled, multiple-dose study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of RG1068 in children with autism and gastrointestinal dysfunction. A total of 129 subjects were randomized; 66 subjects received RG1068 and 63 subjects received placebo. 13 out of the 29 patients for whom PK data were collected received RG1068. Results were not discussed.

Pharmacokinetic studies were not performed in the target population.

In summary, the PK of RG1068 has been evaluated in 18 patients treated with RG1068.

PK parameters from studies 05 and 09 are described in the following table.

Table 2.5-3 Mean Pharmacokinetic Results for Studies of Intravenous RG1068 in Healthy Adult Males

Study	RG1068-05*	RG1068-09
# Patients	6	12 (23 Doses)
PK Sampling Strategy	Sparse sampling	Full PK profile
Age Range (y)	Adult (18-35)	Adult (18-44)
Dose	0.4 µg/kg	0.4 µg/kg
Administration	IV	IV
Elimination Half-Life	3.9 min	2.60 ± 0.16 min
C _{max} (obs)	5.09 ng/mL	4.35 ± 0.40 ng/mL
T _{max} (obs)	2 min**	2.26 ± 0.18 min
AUC (0 - t)	39.0 ng - min/mL	20.8 ± 1.3 ng - min/mL
AUC (0 - infinity)	41.8 ng - min/mL	21.3 ± 1.4 ng - min/mL
Plasma Clearance CL _p (obs)	9.6 mL/min/kg	1.77 ± 0.17 L/min or 21.4 ± 2.1 mL/min-kg
Volume of Distribution V _d (obs)	53.7 mL/kg	6.71 ± 0.83 L or 81.1 ± 10.0 mL/kg

Source: Section 2.7.2, Table 2.7.2.4, Module 2; Individual CSRs, Module 5

* Samples collected using a sparse sampling protocol; therefore individual PK determinations were not possible. PK values reported are the result of using average plasma secretin values for a given time point across the patient group as a whole.

** T_{max} is first measured time point

- **Absorption**

N/A

- **Bioequivalence**

N/A

- **Food interaction**

N/A

- **Distribution**

The plasma protein binding of R1068 is not described.

R1068 has a volume of distribution of 6.71 ± 0.83 L suggesting negligible distribution into tissues.

Therefore, justification about why RG1068 is dosed according to weight is needed. **(This issue is raised in other concerns)**

- **Elimination**

The metabolism of RG1068 has not been studied in microsomes or other ADME based study using biomaterials. Following a single IV dose the plasma elimination half-life of RG1068 was approximately 2 to 4 minutes. R1068 demonstrates rapid plasma clearance in clinical studies. The mean plasma clearance is 1.77 ± 0.17 L /min.

- **Dose proportionality, time dependency and variability**

As only one dose was assessed in clinical trials there is no data to evaluate dose proportionality IV. However, data from escalating doses in subcutaneous administration shows dose proportionality that might be extrapolated to IV formulation.

Accumulation of RG1068 does not occur on multiple dosing in study 09 due to its short half-life. No specific variability data on PK parameters was provided by the company, as no population PK studies were performed.

- **Pharmacokinetics in target population and special populations**

RG1068 PK parameters were not evaluated in target population. The applicant assumes that the sampling profile required to assess a peptide with a half-life less than 3 minutes is incompatible with the study procedure (MRCP) in which the patient was placed into the MRI apparatus and image acquisition occurred every minute for the next 10 minutes. In the assessor views these reason is acceptable.

No studies were conducted in patients with renal or hepatic impairment. Hepatic metabolism role in RG1068 elimination is unknown. RG1068 has a very short exposure after a single dose and the metabolism seems to be conducted by circulation peptidases.

Therefore, the assessor does not anticipate safety concerns regarding the lack of assessment in these special populations. Despite of that, this should be acknowledged in the SmPC.

The effect of gender, race, age and weight on PK parameters was not evaluated.

There is no data from use of RG1068 in pregnant women. It is unknown whether RG1068 is excreted in human milk.

Although the applicant assumed that PK data from children in study 01 is not reliable, data from studies indicate that exposure to RG1068 does not essentially differ between adults and children aged 3-6 y.

- **Interactions**

Specific drug-drug interaction studies with RG1068 have not been conducted.

Pharmacodynamics

- **Mechanism of action**

The mechanism of action of RG1068 is known as it mimics physiological human secretin. Secretin stimulates acinal cells of the exocrine pancreas to secrete a bicarbonate-rich fluid into the resting pancreatic ducts that flows into the intestine. Bicarbonate neutralizes the acid thus establishing a pH favourable to the action of other digestive enzymes in the small intestine. Resting pancreatic duct are small, variable and differ little in tissue density or water content from its surrounding structures, resulting in incomplete visualization and limited diagnostic information. The movement of pancreatic fluid into the pancreatic ducts must improve the delineation of both normal and abnormal duct structures when using MRI.

Magnetic resonance cholangiopancreatography (MRCP) is a thick slice MRI acquisition sequence that images the entire pancreatobiliary duct system.

According to the applicant, the secretion of fluid into the pancreatic ducts augments the magnetic resonance imaging signal by increasing both the diameter and T2 signal-to-noise ratio of the pancreatic ducts, improving the visualization and delineation of both normal and abnormal structures and highlighting abnormal fluid collection and leakage.

Therefore, RG1068-stimulated MRCP will expedite and direct therapy, and also reduce the number of patients exposed to other additional diagnostic procedures including ERCP in patients with unexplained pancreatitis.

- **Primary pharmacology**

The phase II study RG1068-15 was a prospective, multi-centre, baseline-controlled phase II trial which enrolled 80 patients with acute or acute recurrent pancreatitis scheduled for ERCP. It was designed to compare the effect of RG1068 on the sensitivity and specificity of MRCP, comparing pre and post-RG1068 stimulated MRCP to a standard of centrally read ERCP image sets (based-truth standard).

The assessment of pharmacodynamic effect after the intravenous administration of 18.5 mcg intravenous infusion of RG1068 or 0.2 mcg/Kg in patients weighting <50Kg, is described as secondary endpoint.

The **mean change in main pancreatic duct (MPD) diameter** is presented in the following table:

Table 17 **Summary of Baseline and Maximum Post-RG1068 Duct Diameters and Differences (in mm)**

		Baseline		Maximum		Difference				
Segment	N	Mean	SD	Mean	SD	Mean	SD	Lower CI	Upper CI	p-value ^a
Head	80	2.226	1.699	3.777	1.674	1.552	1.370	1.247	1.856	<0.0001
Body	80	2.477	1.993	3.608	1.833	1.131	0.992	0.910	1.352	<0.0001
Tail	80	2.043	1.660	2.965	1.679	0.923	1.062	0.687	1.159	<0.0001

a. The p-value was determined by paired t test.

Abbreviation: CI = confidence interval; SD = standard deviation

Data Source: [Source Table 14.2.8.3.](#)

The mean change in the duct diameter for each pancreatic duct segment after RG1068 infusion was statistically significant and represents between a 45% to 70% increase in dimension.

On average, the maximum duct diameter was obtained at four minutes post-RG1068 for each duct segment.

The **number of complete duct segments identified at each time point** was recorded for ERCP, the baseline MRCP images and ciné MRCP image set (consisted of the baseline MRCP image and all post-RG1068 MRCP images). These data for each MRCP readers are presented in the table below.

Table 18 Number of Duct Segments Visualized

MRCP Reader ^a	Image	Number of Duct Segments Visualized (n=80)					p-value ^a
		0	1	2	3	Total	
1	Pre	9	15	32	24	151	<0.0001
	Ciné	2	8	17	53	201	
2	Pre	21	14	26	19	123	0.0003
	Ciné	2	13	24	41	184	
3	Pre	19	18	28	15	119	<0.0001
	Ciné	1	4	24	51	205	

a. Changes from baseline in the number of duct segments identified were analyzed using a chi-square test.

Abbreviations: MRCP = magnetic resonance cholangiopancreatography

Data Source: [Source Table 14.2.9.3](#)

Significantly more duct segments were visualized in the ciné image set. In addition, over twice as many subjects had complete visualization of the pancreatic duct (i.e. all three duct segments) in the ciné image set as before.

Table 19 Mean Number and Percentage of Duct Segments Identified^a

Study Procedure ^a	Head, n (%)	Body, n (%)	Tail, n (%)
MRCP, Baseline	50.0 (62.5)	49.7 (62.1)	32.3 (40.2)
MRCP, Ciné	71.7 (89.6)	70.7 (88.3)	54.3 (67.9)
ERCP	68.7 (85.8)	63.3 (79.2)	44.7 (55.8)
		p-value^b	
Baseline vs Ciné	0.0098	0.0018	0.0052
Baseline vs ERCP	0.0178	0.0134	0.0534
Ciné vs ERCP	0.6447	0.1123	0.1092

a. Mean number of segments visualized *completely* for MRCP Readers 1-3

b. The p-value was determined by chi-square analysis

Abbreviations: ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography

Study **RG1068-16** was a multi-center, baseline-controlled, open-label, independent-blinded reader, single dose phase III study to confirm the increased sensitivity of RG1068-enhanced MRCP compared to unenhanced MRCP without loss of specificity using ERCP-based truth standard. 258 patients were enrolled. The administered dose of RG1068 was 22.5 mcg/Kg or 0.2 mcg/Kg for subjects weighting < 50 Kg.

The **diameter of each pancreatic duct segment** (head, body and tail) for the pre- and best post-RG1068 images were measured at its midpoint by a single radiologist. The ability to visualize each duct segment for the baseline and ciné image sets was assessed independently by three central blinded radiologists experienced in MRCP.

The tables below summarize the results.

Table 14.2.8.1
Descriptive Statistics of Duct Diameter Data Pre-RG1068

Summary of Pre-RG1068 Assessment					
Parameter	n (Subjects)	Mean (mm)	std	Lower CI	Upper CI
Head	180	2.83	1.15	2.67	3.00
Body	175	2.59	1.26	2.40	2.78
Tail	166	2.09	1.15	1.92	2.27

Table 14.2.8.2
Descriptive Statistics of Duct Diameter Data Best Post-RG1068

Summary of the Best Post-RG1068 Assessment					
Parameter	n (Subjects)	Mean (mm)	std	Lower CI	Upper CI
Head	188	3.26	1.15	3.10	3.43
Body	186	2.83	1.36	2.63	3.03
Tail	181	2.18	1.07	2.02	2.34

Table 17 **Changes in Duct Diameter with the Administration of RG1068**

Duct Segment	N	Mean (mm)	SD (mm)	P value ^a
head	145	0.53	0.97	< 0.0001
body	141	0.4	1.04	< 0.0001
tail	133	0.26	0.79	0.0003

a paired t-test

Abbreviations: SD = standard deviation

Data source: [Table 14.2.8.3](#)

Mean increases in duct diameter (pre-to-post-RG1068) are 0.53 mm, 0.40 mm and 0.26 mm for the head, body and tail of the main pancreatic duct, respectively. These differences correspond to approximately 19.4%, 15.7%, and 12.9% increases, respectively, over the pre-RG1068 diameters based on ratios of means.

Results from RG1068-16 study were re-read (**Study RG1068-16 re-read**) by different MRCP readers from those in prior studies (Study RG1068-15, RG1068-16). The applicant exposed the results about the number duct segments identified after the re-assessment.

Table 15 summarizes **the number of pancreatic duct segments** (head, body and tail) visualized by baseline and RG1068-ciné. Table 24 summarizes the number of pancreatic duct segments visualized after the re-reading study (the same data, different readers).

Table 15 Number of Pancreatic Duct Segments Visualized by MRCP Pre-RG1068 and RG1068-Ciné; number of subjects

Reader	Number of Segments Visualized Pre-RG1068	Number of Segments Visualized on RG1068-Ciné				P value ^a
		0	1	2	3	
1 (131809)	0	11	3	14	19	< 0.0001
	1	0	3	18	31	
	2	0	0	23	71	
	3	0	0	5	50	
2 (945973)	0	27	16	19	19	< 0.0001
	1	5	13	28	17	
	2	1	1	30	33	
	3	0	0	13	26	
3 (950781)	0	2	2	1	11	< 0.0001
	1	1	3	4	20	
	2	0	2	6	35	
	3	0	0	5	156	

a Stuart Maxwell χ^2 test for trend

Note: Light shading indicates the number of subjects in whom a greater number of duct segments were visualized on RG1068-ciné. Darker shading indicates the number of subjects in whom the same numbers of duct segments were detected on both the pre-RG1068 and RG1068-ciné, and no shading indicates the number of subjects in which the baseline visualization was superior.

Data Source: Table 14.2.9.3

Table 24 Number of Pancreatic Duct Segments Visualized by MRCP Pre-RG1068 and RG1068-ciné Image Sets; number of patients

Reader	Number of Segments Visualized Pre-RG1068	Number of Segments Visualized on RG1068-Ciné Image Sets				P value ^a
		0	1	2	3	
1	0	2	3	14	9	< 0.0001
	1	1	5	13	20	
	2	2	3	34	44	
	3	0	0	14	79	
2	0	0	0	0	0	0.1501
	1	0	0	0	1	
	2	0	0	0	2	
	3	0	2	4	224	
3	0	0	2	3	5	< 0.0001
	1	0	6	26	17	
	2	1	10	39	39	
	3	0	2	10	71	

a Stuart Maxwell χ^2 test for trend

Note: Light shading indicates the number of patients in whom a greater number of duct segments were visualized on RG1068-ciné image sets. Darker shading indicates the number of patients in whom the same numbers of duct segments were detected on both the pre-RG1068 and RG1068-ciné image sets.

Data Source: Table 2.2

The applicant should discuss the cause of mismatched results regarding the mean increases in duct diameters between study 15 and 16 (45% to 70% and 13% to 19% respectively). Re-assessed data of

change in duct diameters in the RG1068 re-read study was not presented. The applicant should submit and discuss these results.

- **Secondary pharmacology**

No clinical data on secondary pharmacology are available.

- **Pharmacodynamic interactions with other medicinal products or substances**

No specific in vivo or in vivo interaction studies have been performed. In pivotal studies 15 and 16, the administration of anticholinergic medication (e.g. Bentyl, Cogentin, Atrovent, Sal-tropine Ditropan, Detrol) taken within 24 hours of R1068 dosing was an exclusion criteria, but this issue it was not further discussed.

Conclusions on clinical pharmacology

The application for RG6018 is submitted as an application for a new active substance for diagnostic use with and a full characterization of the pharmacokinetics is therefore warranted. The pharmacokinetic documentation for RG6018 is poor and coming from 3 different studies, being 2 of them (05 and 09) pivotal for the proper characterisation of the PK of the drug. However, the PK profile is described mainly based on PK parameters from only one of them (study 09).

RG1068 is dosed as an intravenous solution and rapidly achieved maximum plasma concentrations at approximately 2.26 ± 0.18 minutes following IV infusion. The plasma protein binding of R1068 is not described. The elimination half-life of RG1068 is 2.60 minutes. RG1068 metabolism data is not available. The applicant stands that RG1068, as a small peptide with very short exposures after single dose, appears to be metabolized primarily by circulation peptidases. The mean plasma clearance is 1.77 ± 0.17 L /min and the volume of distribution of 6.71 ± 0.83 L suggesting negligible distribution into tissues. Therefore, justification about why is dosed according to weight is needed.

RG1068 PK parameters were not evaluated in target population. The applicant assumption that the sampling profile required to assess a peptide with a half-life less than 3 minutes is incompatible with the MRCP is reasonably. No DDI-studies with RG1068 were conducted.

Although the applicant assumed that PK data from children in study 01 is not reliable, data from studies indicate that exposure to RG1068 does not essentially differ between adults and children aged 3-6 y.

The mechanism of action of RG1068 is known as it mimics physiological human secretin. Secretin stimulates acinar cells of the exocrine pancreas to secrete a bicarbonate-rich fluid into the resting pancreatic ducts that flows into the intestine. Resting pancreatic duct are small, variable and differ little in tissue density or water content from its surrounding structures, resulting in incomplete visualization and limited diagnostic information.

Magnetic resonance cholangiopancreatography (MRCP) is a thick slice MRI acquisition sequence that images the entire pancreatobiliary duct system. According to the applicant, the secretion of fluid into the pancreatic ducts augments the magnetic resonance imaging signal by increasing both the diameter and T2 signal-to-noise ratio of the pancreatic ducts, improving the visualization and delineation of both normal and abnormal structures and highlighting abnormal fluid collection and leakage.

Assessment of structural delineation depends on the number of duct segments that can be visualized (head, body, tail), and the extent to which those ducts segments can be seen. The mean change in the duct diameter for each pancreatic segment in study RG1068-15 after RG1068 infusion was statistically significant (mean differences from baseline to maximum duct diameters of 1.55mm, 1.13mm and 0.92mm in head, body and tail segments respectively) It represents between a 45% to 70% increase in

dimension in duct diameters. However, according to the RG1068-16 results, mean increases in duct diameters were 19.4%, 15.7% and 12.9% over the pre-RG1068 diameters (mean differences of 0.53mm, 0.4 mm and 0.26mm in head, body and tail segments respectively). The applicant should discuss the cause of mismatched results regarding the mean increases in duct diameters between study 15 and 16 (45% to 70% and 13% to 19% respectively). Furthermore, re-assessed data of change in duct diameters in the RG1068 re-read study should be submitted and discussed.

The improvement in the number of pancreatic duct segments that can be visualized (head, body, tail) by the MRCP post RG1068 administration in study 15 and 16, added value to the assessment of structure delineation.

No specific in vivo or in vivo interaction studies have been performed. However, the assessor considers the concomitant use of anticholinergic agents as a potential pharmacodynamic interaction. Therefore, it should be discussed by the applicant and reflected in the SmPC.

Clinical efficacy

Dose-response studies and main clinical studies

The assessors consider that, from the data provided by the company to support efficacy, there is a single pivotal study (i.e. RG1068-RR). Then, CPMP/EMA/2330/99, CPMP/EWP/1119/98/Rev) and EMEA/CHMP/EWP/321180/2008 apply. The phase III study was performed in centers in North America but not in Europe.

No clinical studies have been performed aimed to establish either the optimal dose and optimal method of administration of RG1068 or the optimal timing for image acquisition. The company decided to administer the full vial of RG1068 in patients weighing ≥ 50 kg (i.e. a dose range between 0.13 and 0.45 $\mu\text{g/kg}$) and a dose based on body weight at 0.2 $\mu\text{g/kg}$ in patients weighing < 50 kg. The dose used in the pivotal study RG1068-RR was based on previous experience with other secretins (human or porcine) as well on the safe use of RG1068 in trials for other indications at single/repeated doses of 0.4 $\mu\text{g/kg}$ or higher.

Summary of main efficacy results

There is only one pivotal study in this dossier: Study **RG1068-16RR**.

The following table summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for RG1068-16RR trial

Study RG1068-16RR: A post-hoc analysis of a phase III study to evaluate diagnostic performance of RG1068-enhanced MRCP versus unenhanced-MRCP.		
Study identifier	RG1068-16RR	
Design	A multicenter, baseline-controlled, single-dose, Phase III study designed to demonstrate higher sensitivity without sacrificing specificity for detection of pancreatic duct abnormalities by RG1068-enhanced MRCP, in comparison to unenhanced MRCP, on the basis of an ERCP-based truth standard diagnosis .	
	Duration of main phase:	not applicable
	Duration of Run-in phase:	
	Duration of Extension phase:	

Hypotheses	The observed specificity of RG1068-enhanced MRCP is not inferior to that of the unenhanced MRCP with a non-inferiority margin of -7.5%.	
Treatments groups	270 patients with history of acute (recurrent) pancreatitis scheduled for ERCP with pancreatography	Participants received 25 micrograms (if weighing 50 kg or greater) or 0.2. micrograms/g body weight (if weighing less than 50 kg) as a single intravenous injection over 30 seconds followed by a 10 ml normal saline flush over 30 seconds.
Endpoints and definitions	Primary Endpoint: Within-patient sensitivity and specificity for 4 clusters of 10 predefined abnormalities in unenhanced MRCP and RG1068-enhanced MRCP versus the same abnormalities and clusters in ERCP-based truth standard (i.e. ERCP images supplemented by the local <u>ERCP report</u> , plus a report from at least one of the following: <u>CT of the pancreas</u> , <u>KUB radiographs</u> , or <u>EUS</u> , if available).	
Database lock	The first 258 patients with acute (recurrent) pancreatitis scheduled for ERCP with pancreatography.	
Results and Analysis		
Analysis description	Primary Analyses	
Analysis population	Those patients with at least one T2-weighted pre-dose and one T2-weighted post-dose MRCP image (each with one or more segments of the pancreatic duct within the field of view), which the central MRCP reader deemed interpretable, and for which there is a corresponding evaluable ERCP-based truth standard.	
Descriptive statistics	<p>Statistical analysis: The co-primary endpoints were assessed for differences in sensitivity and specificity between the baseline and RG1068-ciné image sets using a paired t-test. The confidence interval for the differences was also estimated for specificity. The non-inferiority margin for specificity was set at -7.5%. The study would be deemed positive if 2 of 3 readers meet the set criteria.</p> <p>Sensitivity was defined as the proportion of pancreatic duct abnormalities defined in the ERCP-based truth standard that were also present on MRCP. Effectiveness was demonstrated for each independent radiologist by a significant improvement in the sensitivity of RG1068-ciné MRCP compared to baseline MRCP values.</p> <p>Specificity was defined as the absence of pancreatic duct abnormalities on the ERCP-based truth standard that were also absent on MRCP. The co-primary endpoint was a non-inferiority demonstration for each reader of RG1068-ciné MRCP and baseline values for specificity, defined as a lower 95% confidence limit of -7.5% for change.</p> <p>Sensitivity and specificity were calculated using a clustered abnormality, within-patient analysis. Clusters are clinically related groups of abnormalities, such that the 10 abnormalities are represented by 4 clusters. For each patient, sensitivity and specificity were calculated by determining the item for item presence and absence of abnormalities based on the truth standard, which were then averaged in each cluster, and clusters were averaged for the within-patient total. The results for each MRCP reader are the summed results for each evaluable patient. Table 3 (in section “Outcomes/endpoints” of the clinical assessment report) summarizes individual abnormalities and their organization into clusters. Specific definitions of each abnormality for MRCP and ERCP were established.</p> <p>Participant flow: A total of 258 subjects were enrolled in the study, 236 with evaluable ERCP and 216-288 with evaluable MRCP depending on the central reader. There were 19 major MRCP acquisition protocol violations in 16 patients.</p>	
Effect estimate per comparison	Primary Endpoint (Sensitivity analysis)	A statistically significant higher sensitivity (clustered by-abnormality, within-patient) of RG1068-enhanced MRCP versus unenhanced MRCP in all three individual readers

	Primary Endpoint (Specificity analysis)	A difference margin in specificity (clustered by-abnormality, within-patient) was lower than 7.5% for RG1068-MRCP compared versus unenhanced MRCP for all three individual readers
Analysis description	For Secondary analyses (image quality and reader confidence) see clinical assessment	

Clinical studies in special populations

No studies in special populations were conducted.

Analysis performed across trials (pooled analyses AND meta-analysis)

Additional evidence of efficacy is presented from phase II study RG1068-15 and from two independent sources as supportive: the Indiana University Database (IUDB) and a meta-analysis. The company presents a comparison and analyses of results across the phase III re-reading study, the phase II study and the IUDB. The metaanalysis is presented separately. As previously mentioned, the results of the original study RG1068-16 are considered by the company as unreliable and the company did not integrate them in the pooled analysis.

Study RG1068-15, the Phase II study, had the same inclusion criteria, imaging acquisition parameters and standardization, study design and controls, and statistical methodology for analysis of primary and secondary endpoints than study RG1068-16RR. Other than sample size, protocol changes between the two studies were minor refinements. In this study, 80 patients were enrolled at 15 sites. RG1068 was administered as an IV dose of 18.5 µg (or 0.2 µg/kg for patients weighing <50 kg). Site-obtained ERCP, baseline MRCP and RG1068-stimulated MRCP images were analyzed by blinded central readers, 3 endoscopists for the ERCP based truth standard and 3 independent radiologists for MRCPs. The sensitivity and specificity of MRCPs were estimated; additionally reader confidence, image quality and structural delineation of pancreatic ducts were also assessed.

IUDB Study was a prospectively defined, blinded read of MRCP images with and without secretin from patients with suspected pancreatic disease or abnormalities. Based on predefined entry criteria, eligible cases were chosen from over 800 S-MRCP examinations performed at Indiana University Hospital from January 2003 to May 2005 and entered into its electronic database. Similar to the RG1068 studies, each case had MRCP images both pre- and post-secretin, and a contemporaneous ERCP. The ERCP based truth standard was determined by a prospective, blinded consensus of two endoscopists, and the MRCP image assessment was completed by a single blinded radiologist. The image analysis consisted of quantitative assessments of duct segments visualized and duct diameters, qualitative assessment of image quality, and lastly, comparison of MRCP sensitivity and specificity in detecting duct abnormalities with and without secretin, using the matched ERCP as the standard. A small proportion of images in each study were unevaluable mainly because of unacceptable ERCP and MRCP images.

Pooled Data Analysis

The pooled efficacy analyses were performed combining data from the two similarly designed, well-controlled RG1068 studies: RG1068-15 (supportive Phase II) and RG1068-16RR (pivotal Phase III). In general, there is very consistent agreement across studies for all endpoints and treatment effect.

Comparison of Results in Sub-Populations

Race was not analyzed as the preponderance of study participants (89%) were Caucasians.

Therefore, pooled data were analyzed to assess the consistency of results across age-, gender-, dose-, and site enrolment-related subgroups. These factors do not seem to influence the primary endpoints (sensitivity and specificity). An analysis of factors known to influence secretin effect (pancreatitis severity and duration) was not performed.

META-ANALYSIS

A literature review and meta-analysis were performed to critically and quantitatively review the available literature on the safety and efficacy of S-MRCP in the assessment of pancreaticobiliary structures. A total of 195 references published from January 1994 to January 2011 were identified. A total of 76 articles met the eligibility criteria and were included in the safety analysis; of these, 18 were suitable for the efficacy analysis. Rigorous prospectively-defined meta-analytic methods were used to combine the data regarding the efficacy of secretin use in conjunction with MRCP across these independent studies.

The primary outcome parameters in the analysis of efficacy were the number of main pancreatic duct segments identified on MRCP before and after secretin administration and the diameter of these segments. The secondary outcome parameters included the overall quality of images before and after secretin administration and the sensitivity and specificity with which secretin-enhanced MRCP was able to detect pancreatic duct abnormalities relative to MRCP or computed tomography (CT) using ERCP or CT-based findings, respectively, as the "truth" standard.

The results of this meta-analysis demonstrated that S-MRCP consistently and significantly improves image quality and delineation of pancreaticobiliary structures relative to MRCP. In a small number of reports, secretin-enhanced MRCP also improved the sensitivity for detection of pancreatic duct abnormalities relative to MRCP or CT. Specificity was relatively unchanged when comparing secretin-enhanced MRCP to MRCP with ERCP as the truth standard and slightly higher for secretin-enhanced MRCP compared to CT.

Supportive study(ies)

STUDY RG1068-15

Please, see details of this study hereinabove.

Discussion on clinical efficacy

The company contends that the clinical utility of RG1068-enhanced MRCP has been demonstrated by the findings in two key studies (phase II RG1068-15 and phase III RG1068-16RR), supported by the retrospective database analysis of the Indiana University and a metaanalysis of the published literature. There is only one pivotal study (i.e. RG1068-RR) to base this application, and then the points to consider for submitting a single pivotal study in support of marketing authorization should be followed (CPMP/EMA/2330/99). The "Guideline on Clinical Evaluation of Diagnostic Agents" (CPMP/EWP/1119/98/Rev 1) and Appendix 1 on Imaging Agents (EMA/CHMP/EWP/321180/2008) also apply.

The proposed indication is "SecreFlo injection is indicated for use with magnetic resonance imaging (MRI) to improve pancreatic duct visualization for the detection of duct abnormalities to enhance clinical decision making in adults with known or suspected pancreatitis."

The proposed posology to be administered is 25 micrograms (if weighing 50 kg or greater) or 0.2. micrograms/kg body weight (if weighing less than 50 kg) as a single intravenous injection over 30 seconds followed by a 10 ml normal saline flush over 30 seconds.

Design and conduct of clinical studies

The original phase III RG1068-16 is not presented as evidence of efficacy as initially intended, since readers' performance was below requirements and quality control was only sloppily adhered to. A re-reading of this study images using new qualified readers and new quality monitoring of the process by a new central imaging lab is currently presented as the pivotal evidence instead (the so-called re-reading study RG1068-16RR).

Re-reading implies a repeated analysis of the same data by a new panel of readers (i.e. a multiple comparison), which would have not been performed if the outcome of the first reading were acceptable. Then, fulfilment of some bias avoidance measures should be assured for re-reading of images of the original trial to be acceptable. To this regard, as stated in the previous advice, readers should be blinded to the confidentiality of the images (and all other data) of the original study and the readers training should be performed with a completely independent data set. Blinding of readers to both the study design and the study protocol of the re-reading study is also of paramount importance. Videotapes and transcripts of the training sessions and signed affidavits (mentioned in page 96 of the protocol) and also the complete documentation of audits conducted by the company should be provided for verification that all these three measures were fulfilled to avoid biases.

The company has requested Scientific Advice four times to EMA in connection to this RG1068 development plan. Former advices found the proposed cluster-based methodology to calculate the primary endpoints (i.e. sensitivity and specificity for baseline MRCP and enhanced MRCP) in the study RG1068-16 to be systematically biased, having a potential undesirable effect on statistical testing and conclusions. The company was advised to choose another method for evaluation of sensitivity and specificity which involved unbiased estimators. For this, it was highly recommended to express test performance in a binary measure on a per-patient level, reflecting the need to show a benefit in clinical decision making. It was actually recommended to use a "less complicated, more readily interpretable and more clinically relevant measures as is the correct prediction of the need for therapeutic intervention". In connection to this, demonstration of an improved negative predictive value for the enhanced MRCP over unenhanced MRCP was considered an important element when it comes to discuss the diagnostic advantages of the enhanced method.

The clinical development hardly adhered to the given EMA advices. For the re-reading study, the company stuck to the same method to calculate the primary endpoints that CHMP thought to be not optimal. CHMP previous recommendations regarding clinically meaningful endpoints to demonstrate improved negative predictive value of enhanced MRCP versus unenhanced MRCP were implemented using an incorrect methodology (as stated in previous advice).

Neither the optimal dose nor the method of administration of RG1068 nor the optimal timing for acquisition of RG1068-enhanced MRCP images were determined by specific studies or adequately justified. The company should further elaborate on it. The dose used in the re-reading study (the same than the one proposed for the product in the SmPC) was based on previous experience with other secretins (human or porcine) under an "off-label" use for enhancing MRCP. However, equivalence of the clinical efficacy among different secretins in the intended indication at the selected dose has not been demonstrated.

Without assessing additional patients in pivotal trials, apart from those recruited in the original phase III study, the company has modified the intended population for RG1068 from adults with acute (recurrent) pancreatitis to adults with known or suspected pancreatitis. No experience in special populations is provided and they should be excluded for the intended use of the product (to be appropriately reflected on the SmPC).

The pivotal trial is the post-hoc analysis of the images from a multicenter, baseline-controlled, single-dose, phase III study aimed to demonstrate the efficacy and safety of RG1068-enhanced MRCP. Subjects in the confirmatory trial ("patients with known acute (recurrent) pancreatitis scheduled for ERCP with pancreatography") are not representative of the population in whom this diagnostic agent is intended to be used (i.e. "patients with known or suspected pancreatitis"). The company should justify that results obtained in the recruited patients could be extrapolated to other populations such as:

- Patient with known chronic pancreatitis
- Patients suspected but not confirmed of any type of pancreatitis
- Patients not scheduled for ERCP with pancreatography

Otherwise, the wording of the indication should be more explicit.

The phase III study was performed in centers in North America. The company should justify that the USA/Canadian population is representative of the EU population regarding the etiology of pancreatitis and their response to secretin, and that similar diagnostic criteria and therapeutic measures are implemented in clinical practice for the management of the intended population.

The protocol did not define standardized criteria (specific signs and symptoms) for the diagnosis of acute (recurrent) pancreatitis in the population to be recruited, and heterogeneity in these criteria among centers and investigators is likely (guidelines by the American Gastroenterological Association; Forsmark et al. 2007). The applicant should provide with the heterogeneity of those criteria in the recruited sample and discuss their potential influence on the study results.

Moreover, the company should justify how selecting patients with known acute (recurrent) pancreatitis scheduled for ERCP with pancreatography applies to European practice in the assessment of the intended population. The reason why the recruited patients had been scheduled for ERCP with pancreatography should be described and if it was appropriately indicated, and if and how other causes of acute (recurrent) pancreatitis had already been excluded.

Restrictions to recruitment of particular populations in this study should be justified, and how this applies to European practice in the diagnostic management of the intended indication. Those are as follows:

- Presence of a pancreatic stent
- Prior history of pancreatic duct drainage procedure
- Prior history of pancreatic resection (Whipple procedure or Whipple variant)

The exclusion of patients with active acute pancreatitis requiring pancreatic rest seems reasonable in order to avoid any reactivation of the pancreatitis in an inflamed pancreas. However, the company should discuss the time period necessary to wait between the initiation of the acute (recurrent) pancreatitis episode and the administration of RG1068 for the use of this product to be considered of acceptable efficacy, also considering the severity of the pancreatitis disease.

Patients sequentially underwent within a 30-day time period a baseline MRCP, a RG1068-stimulated MRCP, and an ERCP procedure. The surrogate standard of truth "ERCP-based truth standard" was composed of the ERCP images plus the local endoscopist (performing the procedure) report plus supplemental reports of additional available diagnostic non-MRCP methods which had been performed anywhere from 120 days prior to RG1068 dosing until just before the ERCP procedure. However, this surrogate standard of truth was neither justified nor standardized among all recruited patients and it may be composed of supplemental information collected long before the trial commenced. EUS is per se an effective and safe diagnostic test and alternative to ERCP in many patients presenting abnormal pancreatic ducts in the many patients with acute/acute recurrent pancreatitis. ERCP is recommended only as a follow-up examination if EUS cannot assist in establishing the diagnosis (Petrone et al. 2008).

The truth standard in this re-reading should have included all relevant data for final diagnosis, as previously recommended. Given the nature of the data discussed (on file since long ago), the standard should have been the reliable final diagnosis of the patients including even the outcome which was already available at re-reading. In this sense, it is important that final diagnosis was not obtained by using unenhanced MRCP or RG1068-enhanced MRCP to avoid any incorporation bias. The company should justify the chosen standard as accurate, close to reality and also as best one for the final diagnosis of the recruited patients in comparison with previous CHMP recommendations.

The choice of the baseline MRCP as comparator has not been justified as appropriate, widely accepted in the EU for the claimed indication and reflecting current medical practice as the guideline of evaluation of diagnostic products requires. The company should provide with extensive review of the literature showing diagnostic performance of baseline MRCP, its widely EU acceptance and its role in the current medical practice in the intended indication and population in which RG1068 is requested approval.

RG1068-enhanced MRCP images were analysed as a ciné set, involving both unenhanced (3) plus enhanced (10) images. This is agreeable as reflecting (later) clinical practice to amend 'enhanced' images with the set of images before secretin administration. However, the second reading of the baseline images (as subset of the ciné image set) might have led to different reading results as compared to the baseline reading (un-enhanced MRCP set). This could lead to wrong interpretation of the diagnostic performance of enhanced MRCP. A CHMP advice for reconsidering the need for keeping the three baseline images in the ciné image set was ignored in the conduct of study RG1068-16RR. The company should discuss the possible influence on the diagnostic performance of RG1068-enhanced MRCP versus unenhanced MRCP caused by the inclusion of the baseline images as part of the ciné- image set.

The primary objective was to demonstrate improvement (i.e. better sensitivity without sacrificing specificity) for detection of pancreatic duct abnormalities by RG1068-enhanced MRCP in comparison to unenhanced MRCP, versus the ERCP-based truth standard. Some issues of technical efficacy of RG1068-enhanced MRCP versus unenhanced MRCP (i.e. better visualisation of the pancreatic duct, better image quality and inter- and intra-reader concordances) were also aimed in this trial. Test-retest reproducibility was not attempted. The flawed secondary objective proposed by the company to assess the clinical utility was however not modified to fully comply with the CHMP recommendations given in previous advices.

Choosing sensitivity and specificity as co-primary endpoints is according to the guideline on the evaluation of diagnostic products. The company unfortunately evaluated sensitivity and specificity using a non-optimal cluster-based methodology and then results of those endpoints are likely biased and difficult to interpret (as also stated by the CHMP during the clinical development of RG1068 and discussed hereinbefore). The primary efficacy endpoint should have been otherwise selected as being clinically relevant according to the guideline (MAJOR OBJECTION 94). However, neither the four predefined clusters nor the selected ten particular abnormalities could be regarded as endpoints having a clinical benefit for the patient. Former previous advices informed that selected endpoints should be the ones that can potentially lead to therapeutic or diagnostic consequences, and the outcome variable recommended as useful was "correct prediction of the need for therapeutic intervention".

The attempted superiority was not clearly defined. For the sample size calculation, the company used a hypothesis related to superiority using a difference in mean sensitivity of 10% between both techniques based on data from phase II. On the other hand, a non-inferiority margin was pre-specified (as -7.5%) but not justified as of clinically relevant in fulfillment of the guideline. The discrepancy between the difference in the margin of sensitivity and specificity should also be justified.

It seems as if extensive and periodic training and retraining of radiologists and endoscopists for being qualified as central readers, even their replacement, was necessary during the conduct of

the re-reading study. The company should discuss how this translates into routine practice. The applicant has not mentioned how they plan to ensure appropriate training and retraining (eg annually) of radiologists and this must be addressed. If so much training is required, it might be because the selected readers had insufficient background or experience (the company is asked to discuss and detail) or because it is almost impossible to detect differences between unenhanced MRCP and RG1068-enhanced MRCP. The conduct of rigorous training and its eventual success will have to be reflected in the SmPC. In general it would be most convincing for generalisability of the results if radiologists and endoscopists selected at the beginning (of the re-reads) provided reading results of constant quality without the need for retraining, replacement and re-qualification.

The company should justify the abnormality detection rate and the agreement rate for the absence of each abnormality which were defined to qualify radiologists and endoscopists as central readers, and the differences in the criteria between radiologists and endoscopists.

As ERCP-based truth standard diagnosis was to be established by the consensus reached by 2 endoscopists reading together, difficulties may arise in case of divergent opinion. The company should explain the procedure followed in those cases in which both endoscopists yielded a divergent opinion. Otherwise, it is unknown why a possible replacement endoscopist reader only assessed ERCP image sets that had not been assessed by the previous reader (i.e. an unqualified (replaced) reader), contrarily to replacement MRCP readers who assessed all MRCP image sets, as it can be assumed that prior assessments might be affected by the unqualified reading. An explanation should be provided.

According to the guideline, observer's concordance and test-retest reproducibility of the diagnostic agent should be assessed. Inter-reader variability was added to the protocol after a previous CHMP advice. Intra-reader variability was designed to be assessed in only 10% of patients. Test-retest reproducibility was not assessed.

The endpoint ERCP prevention index was included in the pivotal in an attempt to assess clinical utility. However, it is not appropriate and does not fully comply with the recommendations given. The clinical usefulness of an MRCP (enhanced or un-enhanced) in the present setting can best be evaluated by the procedure's ability to correctly separate those patients who may benefit from invasive procedures (mainly therapeutic ERCP) from those who have conditions that would not benefit from such procedure. With the acquired data, it would have been possible to determine number of correct predictions of need for further ERCP/no need for further ERCP for un-enhanced and enhanced MRCP applying 1) standard criteria for treatment of the various pathological conditions identified in this setting and 2) a blinded adjudication committee which based on MRCP and other clinical information (excluding ERCP) decides on the need for ERCP. The Company's proposal for calculation of the ERCP prevention index is not correct as stated previously. On the other hand, the company should provide further discussion about the relevant pathologies with high probability of requiring ERCP in the context of the recruited population.

Regarding sensitivity and specificity in patients with chronic pancreatitis, as CHMP previously advised, assessment might be acceptable provided that not only the subset of patients with known chronic pancreatitis (diagnosed based on the ERCP findings) is analysed, but the whole dataset.

This trial has certain particularities, such as not randomizing the order in which the analyzed test is performed and the comparator, contrarily to the recommendations in the guideline. However, considering that the chosen comparator was the unenhanced MRCP study, this lack of non-randomisation might be acceptable. ERCP was protocolised to be performed within 30 days after secretin-enhanced MRCP (S-MRCP). The company should discuss if the 10 predefined duct abnormalities might have changed during this time interval, and discuss the potential influence of any disease change on the study results.

Other particularity is that information to be considered by MRCP readers focused on detailed issues exclusively related to pancreatic ducts even if secretin also influences the biliary flow and allows for visualisation of the biliary tree. The possible impact on the biliary tree visualisation should be assessed.

The company should justify the chosen population for primary endpoint analyses (i.e. those with evaluable ERCP and evaluable MRCP and at least 1 image available on both unenhanced MRCP and enhanced MRCP and in which at least 1 segment is visualized). Any potential bias or limitation to the study results caused by deviation from the intention-to-treat or the per-protocol populations should be elucidated.

Efficacy data and additional analyses

Results are discussed hereinafter on the basis of fulfillment of the "Guideline on Clinical Evaluation of Diagnostic Agents" (CPMP/EWP/1119/98/Rev 1) and Appendix 1 on Imaging Agents (EMA/CHMP/EWP/321180/2008).

TECHNICAL PERFORMANCE AND PRACTICABILITY

RG1068 is a structural analogue of secretin which claims to be used in conjunction with MRCP for imaging the pancreatic duct in adults with known or suspected pancreatitis, as an improvement of unenhanced MRCP. Significant better image quality and better reader confidence of RG1068-enhanced MRCP than baseline MRCP was found in the pivotal re-reading study and the phase II trial

No data on inter- and intra-reader concordance of RG1068-MRCP for the intended indication was adequately established by kappa statistics. Test-retest reproducibility was not even attempted.

DIAGNOSTIC PERFORMANCE

The pivotal re-reading study was focused on evaluating the statistical improvement on sensitivity without sacrificing specificity of enhanced MRCP for detecting clustered pancreatic duct abnormalities by three independent blinded readers, using ERCP supplemented by additional diagnostic non-MRCP reports as reference and an appropriate (although not fully justified) comparator (i.e. unenhanced MRCP). This study has some important methodological drawbacks and limitations (see comments aforementioned), particularly that the endpoints are of not clinical relevance and obtained by a non optimal cluster-based methodology, the standard was neither standardised nor justified as the best one for the final diagnosis of the recruited patients, the comparator is pending to be justified, and that the hypotheses related to superiority of sensitivity and the non-inferiority margin for specificity were not justified.

Consequently, and as anticipated to the company in former CHMP advices, data of sensitivity and specificity of RG1068-enhanced MRCP and unenhanced MRCP obtained in the pivotal trial are difficult to interpret in terms of clinical relevance, even if the primary objective was met (statistically significant higher sensitivity with a difference margin in specificity of less than -7.5% for RG1068-enhanced MRCP compared versus unenhanced MRCP). Moreover, these results are likely biased due to the flaws in the methodology to calculate them in which 10 different abnormalities with different prevalence were distributed in four clusters. Despite any better superiority of RG1068 relative to the comparator (even if questionable), RG1068 did not demonstrate acceptable levels of inferiority when compared to the standard of truth, as required by the guideline.

Considering individual clusters, significantly increased sensitivity was seen in two readers without losing specificity for the particular cluster "pancreas divisum". However, it was shown significantly lower specificity of RG1068-enhanced MRCP than unenhanced MRCP for the cluster "chronic pancreatitis", even if a significant increase of sensitivity was achieved. No significant differences between enhanced and unenhanced MRCP were found in the remaining 2 clusters which had otherwise a lower prevalence.

For each reader, sensitivity of unenhanced-MRCP was significantly higher without losing more than 7.5% of specificity for the overall detection of 10 predefined duct abnormalities. Sensitivities and specificities were expressed for the overall sample and not individualised for the defined 10 abnormalities. However, the prevalence of each of the 10 abnormalities varies much. The most prevalent ones were abnormal side branches (39%), pancreas divisum (25%), irregular (22%) or dilated (18%) main pancreatic duct, and pancreatic duct stenosis (15%). Those with low prevalence were pancreatic cysts (3%), pancreatic duct disruptions (2%) and filling defects (2%) while there were no cases of intraductal papillary mucinous neoplasm.

The same limitations apply to overall sensitivity and specificity results for detection of pancreatic duct abnormalities in the particular subgroup of patients with chronic pancreatitis.

Evaluation of the impact on diagnostic thinking, patient management and clinical outcome has not been adequately performed. This assessment is crucial.

The recruited population size was slightly lower than the estimated one, since an interim analysis detected a higher rate of abnormality prevalence than expected (60.2% vs 50%). The company should confirm whether the interim analysis was planned and how the difference between the intended sample size (270) and the actually recruited one (258) might have influenced the study results. From those recruited 5.84% had a non-evaluable ERCP as expected, but 16 patients had 19 major MRCP acquisition protocol violations. This raises doubts about the actual fulfilment of standards by the clinical sites conducting the trial. All the protocol deviations should be fully detailed, not only those considered by the applicant as major.

Considering that this trial is a multicenter study, it is required to provide with proof of homogeneity, reproducibility and quality of the performances of diagnostic techniques and equipments in different centers.

The Applicant screened only 283, considered for efficacy those 236 with evaluable ERCP but only 216-228 (depending on the central reader) for the primary endpoints. The losses or withdrawals of patients should be justified and any possible bias derived from said losses or withdrawals be described. The efficacy population (n=236) had a slightly higher prevalence of pancreatic duct abnormalities than expected (60.2% presented with at least 1 out of 10 predefined pancreatic duct abnormalities of varying prevalence). It is unknown the final diagnosis of the control group lacking any of the 10 predefined abnormalities. The company should further elaborate on it.

As previously mentioned, the results of the original study RG1068-16 are considered by the company as unreliable and the company did not integrate them in the Summary of Clinical Efficacy. The phase II RG1068-15 trial could be considered as supportive evidence, but it suffered from the same flaws on the study methodology and design, which make results to be of unknown clinical relevance and be likely biased.

Additional evidence of efficacy from two independent sources are presented as supportive, even if obtained with a different secretin product than RG1068 without demonstrating an equivalent clinical effect:

- the Indiana University Database Study that used prospectively defined entry criteria to select patients with acute or acute recurrent pancreatitis from over a retrospective database of 800 S-MRCP examinations previously performed during the period of January 2003 to May 2005
- a comprehensive literature review that systematically examined the use of secretin for the assessment of pancreatic structures by MRCP through January 2011 in clinical practice across diverse centres in Europe and globally. The literature review included studies which have recruited very different populations. Pooled analysis of diagnostic accuracy data is restricted to only two studies accounting for 34 and 81 subjects available to compute sensitivity and specificity respectively. One of these studies was performed on children. Representativeness of diagnostic

accuracy pooled analysis is a concern. Selective reporting cannot be disregarded. The review did not afford the analyses of the clinical impact of performing secretin-enhanced MRCP on a representative sample of patients.

Analysis of the phase II trial results, the retrospective database or of literature data cannot waive a well-designed prospective controlled phase III trial.

EFFICACY IN SUBPOPULATIONS

Subgroup analyses were performed in the pivotal study to investigate the effect of age, gender, dose and clinical site on the diagnostic performance (sensitivity and specificity) of RG1068-MRCP. The influence of those factors seems not relevant.

The company has not provided with the diagnostic performance of the investigation agent from subgroups of patients with different grades of severity and duration of acute pancreatitis. The company should comment as these factors influence the secretin effect.

The applicant should also discuss the impact of disease prevalence in different populations such as ethnic groups, patients with diabetes, etc.

Patients were recruited because of history of acute recurrent pancreatitis or a single episode of acute pancreatitis requiring ERCP with pancreatography. Although all patients had acute (recurrent) pancreatitis, they also presented with mild (n=3.4%), moderate (n=20%) or severe (n=7.6%) chronic pancreatitis. The company should explain why 73 patients with chronic pancreatitis were included, particularly those 18 cases with severe disease whenever it was an exclusion criterion of the protocol.

No paediatric development has been performed. The waiver request was withdrawn by the applicant. The PDCO agreed on a paediatric investigation plan and on the granting of a deferral for RG1068. The plan covers the entire pediatric age range from birth to less than 18 years of age with suspected pancreatic disease (inflammatory, infectious, congenital anomalies, trauma) for a similar indication than in adults.

ARE SPECIAL RISK PATIENTS ADEQUATELY STUDIED TO RECOMMEND DOSE ADJUSTMENTS?

Studies intended to evaluate dose adjustments in special risk patients in which the product is intended to be used (including at least renal impaired subjects, elderly, and, if appropriate, in those clinical settings excluded from the pivotal study) were not conducted.

OVERALL EVIDENCE:

Adequate technical performance has not been demonstrated in accordance with the guideline.

Although significant better image quality and better reader confidence of RG1068-enhanced MRCP than baseline MRCP was demonstrated in the studied population, the first CHMP advice anticipates the company that it is not enough to base efficacy. A diagnostic product has to have a clinical benefit to the patient, not just to allow better visualisation of an anatomical structure. On the other hand, the intra-reader and inter-reader concordance of the experimental technique for the intended indication has not been established as the guideline of diagnostic product requires. Neither has the test-retest reproducibility.

Adequate diagnostic performance (sensitivity and specificity) of RG1068-MRCP for detection of pancreatic duct abnormalities in relation to a standard of truth, and better than that of unenhanced MRCP, have not been demonstrated in well-designed superiority or non-inferiority trials in patients with acute (recurrent) pancreatitis. This is according to the guideline of diagnostic products. Sensitivity and specificity estimates were obtained versus a composite reference standard in a single phase III trial, and compared with those of unenhanced MRCP, by means of a complicated methodology resulting in likely biased results that were,

on the other hand, of unclear meaningful clinical relevance (as identified in all former CHMP advices). Then, this study is not especially convincing according to the guideline of a single pivotal trial.

The product itself may have immediate therapeutic implications and then, in fulfilment with the guideline, relevant impact on diagnostic thinking and/or patient management in the appropriate clinical context should be demonstrated. For this purpose, the company designed a secondary variable (i.e. ERCP prevention index). Results of the ERCP prevention index have no meaningful clinical utility since they were calculated by an incorrect methodology as already mentioned in a previous CHMP advice.

The optimal dose and method of administration of RG1068 and the optimal timing for acquisition of RG1068-enhanced MRCP images, as proposed in the SmPC, has not been well established.

Neither data of clinical efficacy exist nor dose adjustments studies were conducted in special risks populations to allow for recommending the use of the product.

Intended population has been modified during the clinical development of the phase III trials, whenever the recruited population remained constant. This raises doubts regarding the generalizability of the results.

Conclusions on clinical efficacy

Results of sensitivity and specificity for detection of pancreatic duct abnormalities by unenhanced and RG1068-enhanced MRCP in a population with acute (recurrent) pancreatitis are likely biased, difficult to interpret and have unclear clinical meaningfulness. Impact of RG1068 on diagnostic thinking and/or patient management for the intended indication was not adequately assessed. Technical performance was poorly documented (only by image quality and reader confidence but not observers' concordance). Even so, results could not be generalised since recruited patients are not representative of the intended population.

The company did not adhere to former EMA scientific advices given to avoid methodological flaws to calculate sensitivity and specificity as primary endpoints in the pivotal trials, which have likely biased results. Other issues from previous advices were implemented but those aspects regarding clinical utility did not fully fulfil the given CHMP recommendation.

It should be assured and fully documented that training and conduct read in the re-reading study followed acceptable bias avoidance measures.

Clinical safety

Discussion on clinical safety

The exposure to SecreFlo is limited given that only 338 patients were exposed to a single intravenous dose in MRCP/ERCP studies. Other 210 subjects were exposed to iv (from 0.4 to 1µg/kg) or sc (from 10 - 20 µg/kg) administration in studies assessing different therapeutic indications (autism, schizophrenia, obsessive compulsive disorder) as well as 18 healthy volunteers (0.4 µg/kg IV and from 10 to 100µg/kg SC). Nevertheless it should be notice that there is an extensive experience of use of secretin for diagnostic purposes (stimulation of pancreatic secretion and Zollinger's Ellison Syndrome) with other products already available on the market and that, in principle, it is not expected to observe a very different safety profile for the target population of SecreFlo (patients with potential abnormalities in pancreatic duct and known or suspected pancreatitis).

The Applicant has provided an overall summary of adverse events by ERCP patients and MRCP patients, including also AEs for all RG1068 population and placebo subjects. Data related with placebo come from the studies performed in autism and/or other therapeutic indications.

In general more patients in the ERCP group had any adverse event (65.6%) compared to the MRCP group (39%) what is not unexpected. It is known that during ERCP procedure may produce allergic reaction to the contrast dye or have side effects of anesthesia like nausea, breathlessness, dryness of mouth, redness of the skin, blurring of vision, slow pulse rate and fall in blood pressure.

Although the percentage of patients with a related event was higher for patients in the MRCP group (29.9% versus 3.3.%) the proportion of patients with a serious adverse event was higher for subjects undergoing ERCP (20.2% versus 1.8%). Also the percentage of patients with severe AEs was higher for those undergoing ERCP (8.5%) than MRCP (2.1%).

Known common side effects observed with the administration of human secretin include nausea, flushing, abdominal pain and vomiting. Safety data from the pivotal trials show that the commonest AEs for MRCP patients were nausea (13.3%), flushing (8%) and abdominal pain (6.5%). Abdominal pain (18.4%) followed by nausea (14.8%) and vomiting (6%) were the most frequent AEs for patients undergoing ERCP. Vasovagal reactions and transient increase of heart rate have been observed with all the available secretins (biological porcine, synthetic porcine and synthetic human secretin) and could be considered as a class effect that should be properly reflected in the SmPC (see also RMP).

The Applicant has provided data on the occurrence rate of flushing and pancreatitis. Flushing rates were higher for patients undergoing MRCP (8.3%) compared to those undergoing ERCP (0.3%). Pancreatitis is considered as the most frequent complication after ERCP. In unselected series the rate of post-ERCP pancreatitis varies between 5 and 10 %; most of these cases are mild, but some are moderate and less commonly some are severe. Several factors may play a role to induce post-ERCP pancreatitis among them mechanical injury from instrumentation of the pancreatic duct, hydrostatic injury from overinjection, chemical or allergic injury from contrast medium or enzymatic injury from intestinal content. As expected, data provided show much higher rates of pancreatitis in patients undergoing ERCP (16%) than in MRCP-patients (0.9%). The difference was also maintained between the two groups (ERCP and MRCP patients) for serious cases of pancreatitis (14.5% and 0.6%, respectively). The proportion of patients undergoing ERCP with severe pancreatitis was slightly higher than expected as according to published data.

The Applicant has presented the serious pancreatitis cases divided into three categories (pancreatitis, acute pancreatitis and necrotising pancreatitis) being difficult to know what the Applicant is referring to with the term "pancreatitis" compared to "acute pancreatitis". These numbers need to be clarified. Nevertheless taking all cases of pancreatitis together the percentage of ERCP patients with pancreatitis would be 14.5% versus 0.6% for MRCP patients.

No clinically relevant changes are observed in lab and haematological parameters and vital signs.

The Applicant has analysed the safety data by age, gender and weight for both MRCP and ERCP patients. Regarding age, data suggest a better safety profile for older patients (less adverse events like nausea, abdominal pain, flushing, feeling hot as well as pancreatitis). A higher percentage of women reported AEs compared to men both in patients undergoing MRCP and ERCP. (%). These findings are not unexpected given that some risk factors for post-ERCP pancreatitis have been identified in a number of published studies. Among others, younger age and female gender were found to be patient-related predictors.

Finally patients weighing less (<75 kg) suffered less AEs than those weighing more than 75 kg in both groups of subjects (ERCP and MRCP).

There are not data in patients with renal and hepatic impairment. This should be reflected in the SCP.

Immunogenicity testing did not reveal any positive results. However allergic reactions on first time or subsequent use can not be ruled out completely and therefore a suitable warning should be included in the SmPC.

Secretin has been found to be involved in osmoregulation. The applicant should comment how secretin may affect patients with electrolyte and water disturbances and if this should be contraindicated in patients with SIADH. This should also be addressed in the RMP.

Conclusions on clinical safety

Although the exposure to SecreFlo is limited there is an extensive experience of use of secretin for diagnostic purposes with other products already available on the market and, in principle, it is not expected to observe a very different safety profile for the target population of SecreFlo.

The commonest AEs for MRCP patients were those already known for other secretins: nausea (13.3%), flushing (8%) and abdominal pain (6.5%). Most of the AEs were mild and with little clinical relevance. Very few cases of pancreatitis, the most frequent complication for patients undergoing ERCP, were observed in MRCP-patients (0.9%). Data on serious cases of pancreatitis are not totally clear and need to be clarified. No clinically relevant changes are observed in lab and haematological parameters and vital signs.

Immunogenicity tests were performed but specific antibodies to this product were not detected during the clinical development. No hypersensitivity reactions have been described either. Nevertheless SecreFlo is a polypeptide and the risk of hypersensitivity reactions cannot be totally ruled out.

The applicant should comment how secretin may affect patients with electrolyte and water disturbances and if this should be contraindicated in patients with SIADH

There are not data in patients with renal and hepatic impairment what should be reflected in the SCP.

Pharmacovigilance system

The DDPS submitted by Repligen Europe Ltd (version 1.0, dated on March 02, 2012) represents the Pharmacovigilance System that Repligen Corporation operates. Repligen Europe Ltd is its wholly owned subsidiary. A statement regarding the EU-QPPV availability and the means for notification of adverse reaction has been provided in a separate documents by Repligen Corporation and by the EU-QPPV.

Pharmacovigilance activities are conducted by Repligen Corporation (USA) and contracted service providers..

Pharmacovigilance data is archived electronically or on paper and retained indefinitely. Training is tailored to employees' activities and staff grades.

Regulatory assurance and compliance is regularly monitored internally, and oversight activities and continuous assessment are conducted on service providers regularly after their qualification prior to use.

Some deficiencies have been identified on the DDPS during the evaluation. Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market

Risk management plan

This risk management plan needs to be modified and updated according to EU guidelines and several changes on the SmPC should be done.

The applicant should submit and discuss the non-clinical data. Since according to non-clinical data it is unknown whether human synthetic secretin can cause foetal harm, affect prenatal and postnatal development and the maternal function, these issues should be included in the summary of product characteristics (SmPC), both in the section 4.6 as in the 5.3.

Patient who receive this product and have pancreatic duct obstruction are at risk to develop acute pancreatitis; moreover, the risk of worsening an acute pancreatitis is also plausible. Therefore, acute pancreatitis should be considered as a potential risk. Routine risk minimization measures are suggested for this safety concern: SecreFlo should be contraindicated in patient with "pancreatic duct obstruction" or "acute pancreatitis" and the potential risk for triggering an acute pancreatitis in patient with any kind of pancreatic duct obstruction should be reflected on SmPC.

Considering that SecreFlo is a synthetic 27 amino acid peptide (polypeptide) and it should be administrated as intravenous injection over 30 second; the risk of hypersensitivity reaction should be considered as potential risk.

The risk of "vasovagal reactions" and "transient increase in heart rate" should be reflected on SmPC.

The potential interactions of SecreFlo with anticholinergic medications should be commented by the Applicant and reflected in section 4.5 of the SmPC and the fact that patients who have undergone to vagotomy might be hyposensitive to SecreFlo and thus images collected of the pancreatic duct might be of less use should be reflected on SmPC.

The population not included in development phases (as patients with cystic fibrosis, inflammatory bowel disease, with pancreatic stent, duct drainage, resection, atrophy or significant calcification, patient with metal implants) should be reflected on SecreFlo SmPC.

The table of Pharmacological class effects should be submitted according to EU Template and a summary table of the planned pharmacovigilance activities for each important identified/potential risk and important missing information should be presented.

The RMP should be updated including the suggested proposal and following EU guidelines and templates (including Part II of this EuRMP).

4. ORPHAN MEDICINAL PRODUCTS

The Orphan designation was withdrawn on November 19th, 2010

No medicinal product has been designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

5. BENEFIT RISK ASSESSMENT

Benefits

Beneficial effects

SecreFlo (RG1068) has been developed for MRCP for the detection of pancreatic duct abnormalities. Only one secretin product is approved in Europe for other non-imaging diagnostic purposes related to the pancreas, and it is "off-label" use to some extent for enhancing MRCP.

MRCP is a noninvasive technique for evaluating the intrahepatic and extrahepatic bile ducts and the pancreatic duct. Unlike ERCP, MRCP does not require contrast material to be administered into the ductal system. Thus, the morbidity associated with endoscopic procedures and contrast materials is avoided.

From the results achieved in the pivotal trial, it seems that addition of RG1068 to MRCP increases sensitivity without losing specificity for detecting clustered pancreatic duct abnormalities. Image quality and reader confidence were better with enhanced-MRCP.

Uncertainty in the knowledge about the beneficial effects

Addition of RG1068 to MRCP has proven to increase sensitivity versus unenhanced MRCP in a single pivotal trial consisted of a post-hoc analysis (i.e. re-reading of images) of the unreliable original phase III trial. Re-reading of images is problematic, since it would have not been performed if the outcome of the first reading were acceptable and consequently the original study would have been accepted as it is. Since the goals of the re-analysis were met, it is required that the company justifies why the second analysis will be the more valuable and meaningful one. Re-reading would not be acceptable unless the company assures and fully document that bias avoidance measures related to new readers blinding and training were fulfilled. Otherwise, results are likely biased.

Clinical efficacy in the re-reading trial was however assessed in subjects with acute (recurrent) pancreatitis who are not representative of the population in whom the diagnostic agent is intended to be used.

The results of sensitivity and specificity of RG1068 from the pivotal trial are very limited and have unclear clinical relevance. The clinical usefulness of an MRCP (enhanced or un-enhanced) in the present setting should have been evaluated by the procedures ability to correctly separate those patients who may benefit from invasive procedures (mainly therapeutic ERCP) from those who have conditions that would not benefit from such procedure.

A major feature of MRCP is that it is not a therapeutic procedure, whereas ERCP is used for diagnosis and treatment. The impact of this is that if ERCP is necessary after MRCP as a therapeutic intervention, MRCP could have been avoided and patients would be able to proceed immediately to treatment. However, if no therapeutic intervention is found to be necessary, MRCP avoids the potential morbidity and mortality associated with ERCP.

Other particularity is that information to be considered by MRCP readers focused on detailed issues exclusively related to pancreatic ducts even if secretin also influences the biliary flow and allows for visualisation of the biliary tree. This potential value is not considered at all.

Actual need for the S-MRCP will be restricted to few cases in the management of patients with acute pancreatitis. Once a diagnosis of acute pancreatitis is made, additional tests are needed to determine the underlying cause. Gallstone and alcoholism account for 75% of the cases, and are easily detectable by history data, serum levels of some parameters, an abdominal ultrasound. Only in some patients extensive or invasive evaluation is recommended by means of different techniques (endoscopic ultrasound (EUS), CT, ERCP, MRCP). Secretin is not needed for enhancing MRCP images in all cases, since unenhanced MRCP provides accurate depiction and measurements of the bile and pancreatic ducts in a high percent of examinations. Up to now, it is unknown in which particular place of the diagnostic algorithm for the intended population RG1068 both is intended in clinical practice and was assessed in the pivotal trial.

Risks

Unfavourable effects

Although the exposure to SecreFlo is limited there is an extensive experience of use of secretin for diagnostic purposes with other products already available on the market and, in principle, it is not expected to observe a very different safety profile for the target population of SecreFlo.

The commonest AEs for MRCP patients were those already known for other secretins: nausea (13.3%), flushing (8%) and abdominal pain (6.5%). Most of the AEs were mild and with little clinical relevance. Very few cases of pancreatitis, the most frequent and well-known complication for patients undergoing ERCP, were observed in MRCP-patients (0.9%). No clinically relevant changes are observed in lab and haematological parameters and vital signs.

It seems as if extensive and periodic training and retraining of radiologists and endoscopists for being qualified as central readers, even their replacement, was necessary during the conduct of the re-reading study. If so much training is required, it might be because the selected readers had insufficient background or experience or because it is almost impossible to detect differences between unenhanced MRCP and RG1068-enhanced MRCP. In general it would be most convincing for generalisability of the results if radiologists and endoscopists selected at the beginning (of the re-reads) provided reading results of constant quality without the need for retraining, replacement and re-qualification. Anyway, if extensive ad hoc training of the image readers is necessary to detect a small difference between unenhanced MRCP and RG1068-MRCP, the real impact of RG1068 on diagnostic thinking and patient management would be questionable.

Uncertainty in the knowledge about the unfavourable effects

It is not possible to evaluate the effect of misdiagnosis when assessing endpoints which have no clinical relevance.

Data on serious cases of pancreatitis are not totally clear and need to be clarified.

Vasovagal reactions and transient increase of heart rate have been observed with all the available secretins (biological porcine, synthetic porcine and synthetic human secretin) and could be considered as a class effect. A mention should be done in the SmPC.

Immunogenicity tests were performed but specific antibodies to this product were not detected during the clinical development. No hypersensitivity reactions have been described either. Nevertheless SecreFlo is a polypeptide and the risk of hypersensitivity reactions cannot be totally ruled out. This should be included in the SmPC.

SecreFlo has not been studied in patients with renal and hepatic impairment. This should be included in the appropriate section of the SmPC.

Balance

Importance of favourable and unfavourable effects

SecreFlo allows evaluating pancreatic duct abnormalities by a non-invasive technique with better diagnostic performance than unenhanced MRCP. However, the clinical efficacy might likely be biased as obtained by a post-hoc re-reading of images, selecting endpoints of unclear clinical relevance in a population not representative of the intended population. The ability to correctly separate those patients

who may benefit from invasive procedures (mainly therapeutic ERCP) from those who have conditions that would not benefit from such procedure is unknown.

The safety profile for RG1068-enhanced MRCP is much better than for ERCP; however, the effect of misdiagnosis will be unknown until clinically relevant endpoints are assessed.

Benefit-risk balance

For all this above, the benefit/risk ration of RG1068 for the intended indication is **negative**.

5.1. Conclusions

The overall B/R of SecreFlo is negative.

7. APPENDICES

List of references

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