



(43) International Publication Date
19 January 2017 (19.01.2017)

(10) International Publication Number
WO 2017/009136 A1

(51) International Patent Classification:

A61K 38/48 (2006.01) *A61K 38/36* (2006.01)
A61P 13/00 (2006.01) *A61K 38/37* (2006.01)

(21) International Application Number:

PCT/EP2016/065975

(22) International Filing Date:

6 July 2016 (06.07.2016)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

15176848.8 15 July 2015 (15.07.2015) EP

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(81) Designated States (*unless otherwise indicated, for every kind of national protection available*): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY,

BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (*unless otherwise indicated, for every kind of regional protection available*): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) Title: FACTOR XIII FOR THE TREATMENT OF INTERSTITIAL CYSTITIS

(57) Abstract: The present invention relates to the use of a protein in the treatment of interstitial cystitis (IC).



WO 2017/009136 A1

FACTOR XIII FOR THE TREATMENT OF INTERSTITIAL CYSTITIS

FIELD OF THE INVENTION

5 The present invention relates to the use of a protein in the treatment of interstitial cystitis (IC).

BACKGROUND OF THE INVENTION

 "Interstitial cystitis (IC) is a chronic bladder disease, of unknown origin, characterized by symptoms of pain, such as pelvic pain, and lower urinary tract
10 symptoms (LUTS) such as increased urinary frequency/urgency. More recently terminology has evolved to include painful bladder syndrome (PBS) (MacDiarmid SA et al. Rev Urol. 9(1), 9- 16 (2007)) and bladder pain syndrome (BPS) (van der Merve et al. European Urology. 53,60-67 (2008)).

 Prevalence rates of IC vary from 67 to 230 per 100,000 women having clinically
15 confirmed disease, although the number is likely higher than this due to under- or mis-diagnosis, commonly as endometriosis, recurrent urinary tract infection, overactive bladder or vulvodynia (Forrest J B et al. Clinical Courier. 24(3), 1-8 (2006)). IC has a significant impact on quality of life, affecting travel, family relationships, and employment (Slade D et al. Urol 1997; 49 (5A Suppl): 10-3), as well as being associated with
20 depressive symptoms (Rothrock N E et al. J Urol. 167, 1763-1767(2002)).

 Although of unknown origin of IC, the Mechanisms behind the disease is believed to be shared with other diseases with increased prevalence in patients with IC. Most notably with inflammatory bowel disease (Crohn's disease and ulcerative colitis), which is more than 100 times more common in patients with IC than in the general population
25 (van der Merve et al. Nature clinical practice. Urology. 4(9), 484-91 (2007))

 IC is a highly debilitating disease resulting in pain and frequent voiding's night and day. 5-50% of patients with IC have macroscopic lesions in the bladder wall named "Hunners lesion". Patients with Hunners lesions are often non responsive to pharmacological treatment; and procoagulation/fulguration (burning of the bladder from
30 the inside 1-3 times per year) is recommended as first line treatment in this subgroup of patients. Although effective, the effect decrease gradually over time (Ryu, J. et al. Korean journal of urology. 54, 767-771 (2013)).

 There is a continuing need to provide a novel, effective treatment for IC without the adverse effects or limited efficacy of currently available therapies. A less invasive, but

equally effective pharmacological alternative to fulguration or to surgery, would significantly improve the convenience of treatment for IC patients.

Plasma derived FXIII has shown beneficial effect on drug-induced haemorrhagic cystitis (Sakuma, H. et al. Rinsho Ketsueki. 35, 279-285 (1994)).

5 Fulguration of the bladder has been shown to be beneficial in IC patients with Hunners lesion (Ryu, J. et al. Korean journal of urology. 54, 767-771 (2013)).

SUMMARY OF THE INVENTION

The present invention is based on the surprising discovery that Factor XIII (FXIII) can be used in the treatment of interstitial cystitis (IC).

10 In one aspect, the present invention provides a pharmacological treatment of IC with a prophylactic or on demand dosing of FXIII.

In another aspect of the invention, there is provided a method for treating or preventing IC, comprising administering an effective amount of FXIII.

15 In an embodiment of the invention, FXIII is recombinant FXIII. One advantage with using recombinant FXIII is that it can be produced in big quantities with minimal risk of pathogen contamination.

In a further embodiment of the invention, FXIII is administered intravenously, intramuscularly, subcutaneously, or directly in the bladder.

20 In another embodiment of the invention, FXIII is administered in combination with another or other haemostatic agent(s), for example Factor II, Factor VII, Factor VIII, Factor IX, Factor X, or pro-coagulant antibodies.

25 Other objects, features and advantages of the present invention will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

BRIEF DESCRIPTION OF DRAWINGS

30 Figure 1 shows the effect of rFXIII in the rat model of interstitial cystitis induced by multiple injections of cyclophosphamide on the inter contraction interval (A) and on the bladder capacity (B).

Figure 2 shows the effect of rFXIII on the intestinal integrity measured as Geboes and Riley histologi scores before and after treatment in patients with Ulcerative Colitis.

DESCRIPTION

The present invention is based on the surprising discovery that Factor XIII (FXIII) can be used in the treatment of interstitial cystitis (IC).

5

Interstitial cystitis

IC is a chronic bladder disease, of unknown origin, characterized by symptoms of pain, such as pelvic pain, and lower urinary tract symptoms (LUTS) such as increased urinary frequency/urgency. Prevalence rates of IC vary from 67 to 230 per 100,000 women having clinically confirmed disease. Pain associated with interstitial cystitis comprise lower abdominal (pelvic) pain; bladder pain; suprapubic pain; vaginal pain; pain in the penis, testicles, scrotum and perineum; urethral pain; dyspareunia; pain, pressure or discomfort that may increase as the bladder fills.

As defined herein, the term IC includes painful bladder syndrome (PBS) and bladder pain syndrome (BPS).

Lower urinary tract symptoms comprise three groups of urinary symptoms, which may be defined as storage (irritative), voiding (obstructive) and post-micturition symptoms. Storage symptoms comprise urgency, frequency, nocturia, urgency incontinence and stress incontinence, which can be associated with overactive bladder (OAB) and benign prostatic hyperplasia (BPH). Voiding symptoms comprise hesitancy, poor flow, intermittency, straining and dysuria. Post-micturition symptoms comprise terminal dribbling, post-void dribbling and a sense of incomplete emptying.

Treatment of IC with FXIII

In an aspect of the invention, there is provided a method of treatment or prevention of IC, comprising administering an effective amount of FXIII.

In an embodiment of the invention, FXIII is reducing the symptoms of interstitial cystitis. In one embodiment of the invention, FXIII is of inhibiting or blocking pain and/or a lower urinary tract symptom (LUTS) associated with interstitial cystitis and/or painful bladder syndrome and/or bladder pain syndrome. In some embodiments, the pain and/or lower urinary tract symptom is/are alleviated within about 1 day after administering FXIII. In some embodiments, the pain and/or lower urinary tract symptom is/are alleviated within about 1 week after administering FXIII. In some embodiments, the pain and/or lower urinary tract symptom is/are alleviated within about 2 weeks after

administering FXIII. In some embodiments, the pain and/or lower urinary tract symptom is/are alleviated within about 8 weeks after administering FXIII.

FXIII transglutaminase activity cross-links Fibrin in the urinary bladder and results in a better barrier function of the urinary bladder. Especially in severe patients with focal lesions removal of the lesioned areas or diversion of the urine have been proven to reverse symptoms.

The term "treatment", as used herein, refers to the medical therapy of any human or other vertebrate subject in need thereof. Said subject is expected to have undergone physical examination by a medical practitioner, or a veterinary medical practitioner, who has given a tentative or definitive diagnosis which would indicate that the use of said specific treatment is beneficial to the health of said human or other vertebrate. The timing and purpose of said treatment may vary from one individual to another, according to the status quo of the subject's health. Thus, said treatment may be prophylactic, palliative, symptomatic and/or curative. In terms of the present invention, prophylactic, palliative, symptomatic and/or curative treatments may represent separate aspects of the invention.

FXIII may be administered parenterally, such as intravenously, such as intramuscularly, such as subcutaneously. Alternatively, it may be administered via a non-parenteral route, such as perorally or topically or by installation directly into the bladder via a catheter. FXIII may be administered prophylactically. FXIII may be administered therapeutically (on demand).

Factor XIII

Blood coagulation Factor XIII (FXIII) is a plasma transglutaminase, also known as "fibrinolygase" and "fibrin stabilizing factor". FXIII is a tetramer composed of two A subunits and two B subunits (A₂B₂). Each subunit has a molecular weight of approximately 80,000 Da, and the complete protein has a molecular weight of approximately 330,000 Da. The A subunits contain a transglutaminase catalytic site, whereas the B subunits have no catalytic activity but act as a structural protein that protect the A subunits from clearance.

The FXIII enzyme is the last enzyme to be activated (to FXIIIa) in the coagulation cascade. FXIIIa functions to cross-link α - and γ -fibrin chains, resulting in a stronger (secondary) clot with increased resistance to fibrinolysis.

Plasma FXIII is dependent on thrombin and Ca²⁺ for its activation. Thrombin cleaves FXIII at the C-terminal side of Arg37 of the A subunits, resulting in the non-activated FXIIIa'. A conformational change in the presence of Ca²⁺ releases the

activation peptide (residues 1-37 of each A subunit) and the B subunits, leaving the active enzyme. Activated FXIII (FXIIIa*) is one catalytically active form of FXIII. (The other catalytically active forms of FXIII is FXIIIa°.)

Zymogen FXIII is also capable of being non-proteolytically activated in the absence of thrombin or other proteases. This activation is solely an effect of a conformation change, without the release of the activation peptide, resulting in rFXIIIa°. This latter activation pathway is dominant for intracellular FXIII when no thrombin is present.

The terms "Factor XIII" and "FXIII" herein encompasses the uncloven zymogen, FXIII, both as the FXIII-A2 dimer and as the FXIII-A2B2 tetramer, the cloven molecule FXIIIa', the activated protease, FXIIIa* and the non-proteolytically activated form of FXIII, FXIIIa°.

As defined herein, FXIII may be a naturally occurring wild-type FXIII, (Ichinose A et al. Biochemistry 1986; 25(22): 6900-6906)), or FXIII may be naturally occurring (wild type) allelic variants thereof. In one naturally occurring allelic variant of FXIII, the amino acid at position 651 is an E. In another naturally occurring allelic variant of FXIII, the amino acid at position 651 is a Q. FXIII(a) compounds may originate from human or other animal sources, e.g. human FXIII, porcine FXIII and bovine FXIII. FXIII compounds of the present invention include the complete FXIII zymogen tetramer (A2B2) and FXIIIa, as well as subunits thereof, including the A subunit.

FXIII of the present invention may be biologically active fragments, derivatives or variants of FXIII that retain at least part of the characteristic cross-linking activity of the wild-type FXIIIa. Such cross-linking activity may be measured by methods known in the art, including the FXIII activity assay mentioned in the examples. In certain embodiments, biologically active fragments, derivatives or variants of FXIII retain at least 10%, such as at least 20%, such as at least 30%, such as at least 40%, such as at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 100% of the cross-linking activity of wild-type FXIIIa.

Fragments, derivatives, and variants of FXIII include substitutional, insertional and deletional variants. Insertional variants comprise amino and/or carboxyl terminal fusions as well as intrasequence insertions of single or multiple amino acid residues. Insertions may, for instance, be introduced within the mature coding sequence of the wild-type FXIII protein. Deletion variants are characterized by the removal of one or more amino acid residues from the wild-type FXIII protein. These variants ordinarily are prepared by site specific mutagenesis of nucleotides in the DNA encoding the protein, thereby producing DNA encoding the variant, and thereafter expressing the DNA in

recombinant cell culture. However, variant protein fragments may also be prepared by in vitro synthesis. While the site for introducing an amino acid sequence variation ordinarily is predetermined, the mutation itself need not be predetermined. For example, in order to optimize the performance of a mutation at a given site, random mutagenesis may be conducted at the target codon or region and the expressed protein variants screened for the optimal combination of desired activity. Techniques for making substitution mutations at predetermined sites in DNA having a known sequence are well known: M13 primer mutagenesis, for example. Substitutional variants are those where at least one residue sequence has been removed and a different residue inserted in its place. Amino acid substitutions are typically of single residues; insertions usually will be in order of about from 1 to 10 amino acid residues; and deletions will range from about 1 to 30 residues. Deletions or insertions may for instance be made in adjacent pairs, i.e., a deletion of 2 residues or insertion of 2 residues. Substitutions, deletions, insertions or any combination thereof may be combined to arrive at a final construct. The mutations created in the DNA that encodes the variant protein must not place the sequence out of reading frame and, preferably, will not create complementary regions that could produce secondary mRNA structures. One example of a genetically engineered variant of FXIII is the Val34Leu variant of wild-type human FXIII (i.e. a variant in which the Val residue at position 34 in the amino acid sequence of wild-type human FXIII is replaced by a leucine residue).

rFXIII has been described to have an anti-inflammatory effect (US005464615A). rFXIII has been demonstrated to increase mucosal healing (WO98/51333).

Use of Factor XIII

In an aspect, the present invention provides a use of FXIII for treatment of IC.

In one embodiment of this aspect, it is IC with or without Hunners lesions.

In an aspect, the present invention provides a use of FXIII for the manufacture of a medicament for the treatment of interstitial cystitis.

Combination treatments

FXIII may be co-administered with one or more other therapeutic agents or formulations. The other agent may be an agent that enhances the effects of FXIII. The other agent may be intended to treat other symptoms or conditions of the patient. For example, the other agent may be a pro-coagulant, a haemostatic agent, an immunosuppressant or an anti-inflammatory agent.

The other agent may be a haemostatic agent, for example a pro-coagulant antibody or another blood coagulation factor protein (e.g. Factor II, Factor VII, Factor VIII, Factor IX or Factor X).

Combined administration of two or more agents may be achieved in a number of different ways. In one embodiment, FXIII and the other agent may be administered together in a single composition. In another embodiment, FXIII and the other agent may be administered in separate compositions as part of a combined therapy. For example, the modulator may be administered before, after, or concurrently with the other agent.

10 **Pharmaceutical formulations**

In another aspect, the present invention provides compositions and formulations comprising FXIII, for the use in the treatment of IC. For example, the invention provides a pharmaceutical composition that comprises FXIII, formulated together with a pharmaceutically acceptable carrier.

Accordingly, one object of the invention is to provide a pharmaceutical formulation comprising FXIII which is present in a concentration from 0.25 mg/ml to 250 mg/ml, and wherein said formulation has a pH from 2.0 to 10.0. The formulation may further comprise one or more of a buffer system, a preservative, a tonicity agent, a chelating agent, a stabilizer, or a surfactant, as well as various combinations thereof. The use of preservatives, isotonic agents, chelating agents, stabilizers and surfactants in pharmaceutical compositions is well-known to the skilled person. Reference may be made to Remington: The Science and Practice of Pharmacy, 19th edition, 1995.

In one embodiment, the pharmaceutical formulation is an aqueous formulation. Such a formulation is typically a solution or a suspension, but may also include colloids, dispersions, emulsions, and multi-phase materials. The term "aqueous formulation" is defined as a formulation comprising at least 50% w/w water. Likewise, the term "aqueous solution" is defined as a solution comprising at least 50 % w/w water, and the term "aqueous suspension" is defined as a suspension comprising at least 50 %w/w water.

In another embodiment, the pharmaceutical formulation is a freeze-dried formulation, to which the physician or the patient adds solvents and/or diluents prior to use.

In a further aspect, the pharmaceutical formulation comprises an aqueous solution of FXIII, and a buffer, wherein FXIII is present in a concentration from 1 mg/ml or above, and wherein said formulation has a pH from about 2.0 to about 10.0.

EXAMPLES**Example 1**

In order to determine whether rFXIII reverse the reduction in bladder capacity and the intercontraction interval in a rat model of interstitial cystitis the following experiment was performed.

Chronic treatment with cyclophosphamide and rFXIII or cyclophosphamide and vehicle was administered to male Sprague Dawley rats for a period of 7 days (D1-D7):

Injection with Cyclophosphamide CYP (Sigma-Aldrich, St-Quentin-Fallavier) intraperitoneally (i.p.) at the dosing of 65mg/kg at D1, D3, D5 and D7

Blinded and randomized intravenous injection via the tail vein of 10 mg/ml, 15mg/kg rFXIII or vehicle every day from D1 to D7.

At D8, animals were anesthetized with isoflurane. The left carotid artery was catheterized with a PTFE catheter filled with heparinized saline (50 UI/ml) for mean arterial pressure (MAP) monitoring. Ureters were then transected and ligated distally to prevent bladder filling with urine during experiments. The bladder dome was exposed via a midline abdominal incision and one polyethylene catheter (PE-50: 0.965 mm OD) filled with saline was inserted within the bladder. The catheter was connected to a pressure transducer for bladder pressure monitoring and to a syringe-pump allowing bladder perfusion. The intravesical pressure was recorded continuously).

A 40-minute post-surgery recovery period was observed before the beginning of the bladder perfusion, during which isoflurane percentage was decreased to reach a lighter level of anesthesia ($\sim 0.7\%$), to avoid confounding effects on micturition. The bladder was then continuously perfused (40 μ l/min) with saline during a stabilization period of 30 minutes. When 2-3 reproducible micturition cycles were recorded during this stabilization period, an evaluation period of 3-5 micturition cycles were recorded. The intravesical pressure was recorded throughout the experiment.

The following parameters of reflex-evoked bladder contractions were measured: Intercontraction interval (s), ICI, intimately correlated to the frequency of voiding contractions Voided volume (μ l), VV, as the release of fluid at the urethral meatus concomitant with a voiding contraction Infused volume (μ l), The bladder capacity was estimated as the VV parameter.

These parameters were measured and averaged for the evaluation period as mean $\pm$ SEM. Comparisons were performed using unpaired student t-test with GraphPad Prism® 5.04 software. P values < 0.05 were considered significant. Inter contraction interval was considered the primary endpoint.

Results are shown in Figure 1 as mean values +-standard error of the mean. n=13. * indicates statistical significance ($p < 0.05$) of the effect of rFXIII vs vehicle treated animals. rFXIII significantly reversed the reduction in bladder capacity (Unpaired t-test: $*p < 0.05$ (0.03), figure 1b) and the inter contraction interval (Unpaired t-test: $*p < 0.05$ (0.03), figure 1b).

This data shows that rFXIII reverses the decrease in bladder capacity and/or the increase in sensitivity to bladder filling, in a non-acute model of chronic interstitial cystitis.

Example 2

In order to determine whether rFXIII would benefit patients with ulcerative colitis, patients were dosed multiple times with rFXIII.

A multi-centre, multi-national, double-blind, randomised, placebo-controlled, parallel group, 2-arm, phase 2a trial designed to assess the effects of rFXIII on mucosal healing in subjects with mild to moderate active UC (i.e., ulcerative colitis disease activity index [UC-DAI]) score of (4–10). Only patients with $\leq 75\%$ of the normal FXIII plasma concentration based on BeriChrom® assay, were included in this trial.

Recombinant factor XIII (rFXIII) was administered as intravenous (i.v.) injections at a dose of 35 IU/kg. The doses were administered once every second week for a total of 4 doses. Placebo formulation was administered as intravenous (i.v.) injections once every second week. The doses were administered for a total of 4 doses. Tissue samples were taken for histological evaluation before and after treatment based on Rileys score, ranging from 0 to 18, and the Geboes score ranging from 0 to 5. Results are presented as the difference in the scores: Post-treatment score – Pre-treatment score. Results are shown in Figure 2 as mean values +-standard error of the mean

Study was terminated earlier than planned because of a high number of screening failures. Samples from 10 patients were histologically evaluated and demonstrated improved mucosal integrity compared to placebo (figure 2).

This data shows that in a double blinded study, rFXIII can improve the mucosal integrity in patients with a disease which is known to be closely related to interstitial cystitis. Furthermore mucosal integrity is known to be key in interstitial cystitis with IC where removal of the compromised tissue or removal of urine by urinary diversion surgery completely reverts all symptoms.

While certain features of the invention have been illustrated and described herein, many modifications, substitutions, changes, and equivalents will now occur to those of ordinary skill in the art. It is, therefore, to be understood that the appended

claims are intended to cover all such modifications and changes as fall within the true spirit of the invention.

CLAIMS

1. Use of Factor XIII for the treatment of interstitial cystitis.

5

2. Use of Factor XIII for the manufacture of a medicament for the treatment of interstitial cystitis.

3. Use of Factor XIII, according to any one of the preceding claims, wherein it is interstitial cystitis with or without Hunners lesions.

10

4. Use of Factor XIII, according to any one of the preceding claims, wherein the Factor XIII is a human Factor XIII.

5. Use of Factor XIII, according to any one of the preceding claims, wherein the Factor XIII is plasma derived Factor XIII or recombinant Factor XIII.

15

6. Use of Factor XIII, according to claims 1-3, wherein Factor XIII is selected from the group consisting of Factor XIII, and biologically active fragments, derivatives, and variants thereof that retain at least part of the characteristic cross-linking activity of the wild-type Factor XIII.

20

7. Use of Factor XIII, according to any one of the preceding claims, wherein Factor XIII is administered intravenously, intramuscularly, subcutaneously, or directly in the bladder.

25

8. Use of Factor XIII, according to any one of the preceding claims, wherein the concentration of said Factor XIII is in the range from 1 mg/ml to about 100 mg/ml.

9. Use of Factor XIII, according to any one of the preceding claims, wherein Factor XIII is administered in combination with another or other pro-coagulant(s), haemostatic agent(s), immunosuppressant(s) or anti-inflammatory agent(s).

30

10. Use of Factor XIII, according to any one of the preceding claims, wherein Factor XIII is administered in combination with another or other haemostatic agent(s).

35

11. Use of Factor XIII, according to claim 10, wherein the another or other haemostatic agent(s) are selected from the group of Factor II, Factor VII, Factor VIII, Factor IX, Factor X, and pro-coagulant antibodies.

- 5 12. Method for treating interstitial cystitis, comprising administering an effective amount of a pharmaceutical composition comprising Factor XIII.

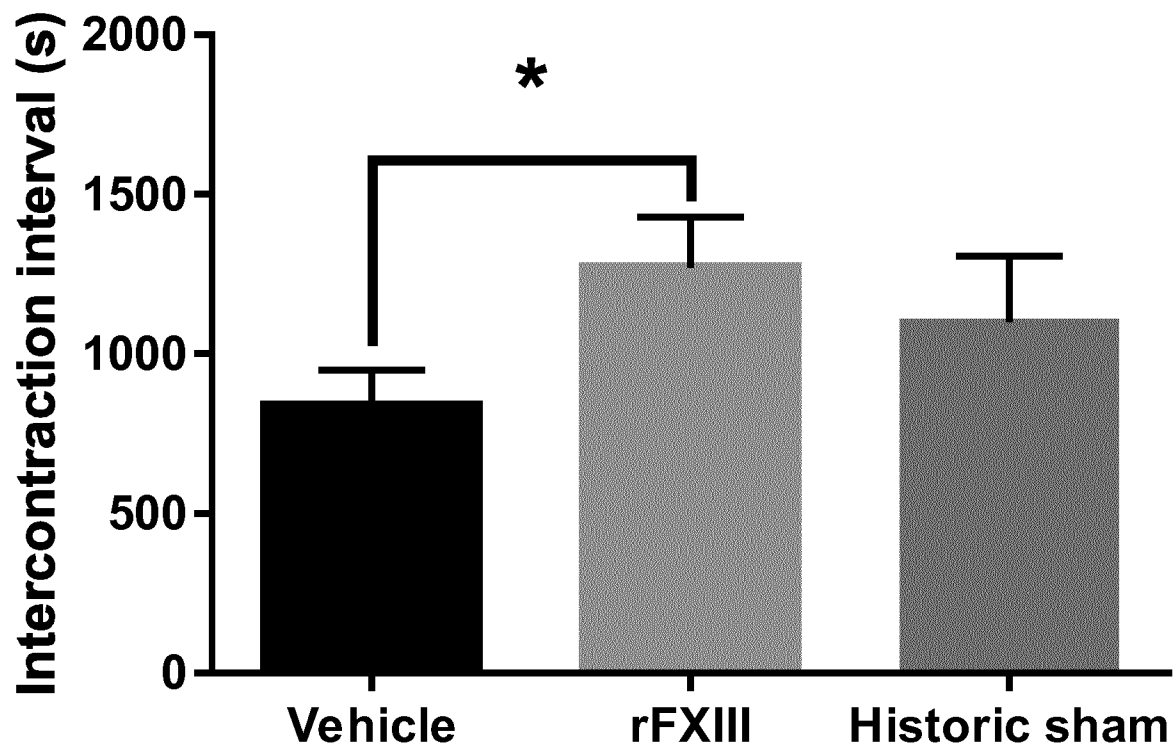


Fig. 1a

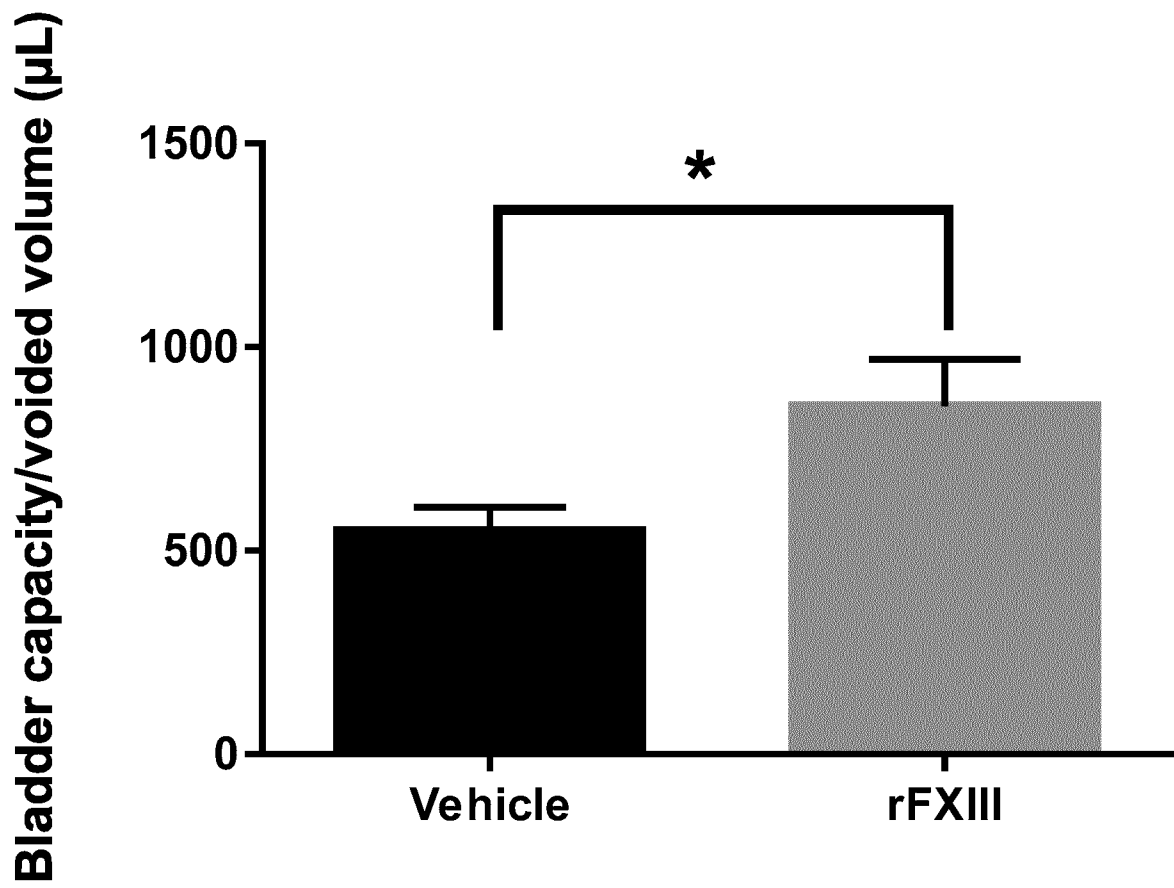


Fig. 1b

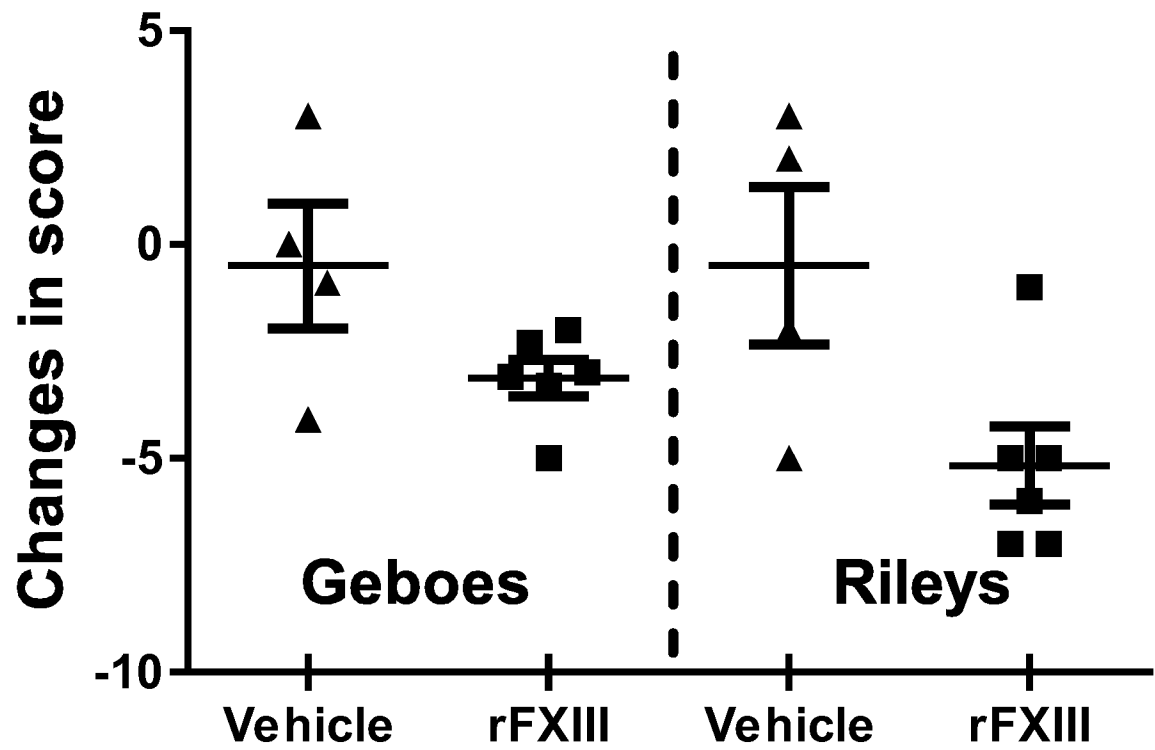


Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/065975

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K38/48 A61P13/00 A61K38/36 A61K38/37
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE, CHEM ABS Data, BIOSIS, Sequence Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HARKENSEE CHRISTIAN ET AL: "Prevention and management of BK-virus associated haemorrhagic cystitis in children following haematopoietic stem cell transplantation--a systematic review and evidence-based guidance for clinical management.", BRITISH JOURNAL OF HAEMATOLOGY SEP 2008, vol. 142, no. 5, September 2008 (2008-09), pages 717-731, XP002750825, ISSN: 1365-2141 abstract page 722, right-hand column, paragraph 1; table 2 ----- -/--	1-12



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

19 September 2016

Date of mailing of the international search report

05/10/2016

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/065975

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 98/51333 A1 (ZYMOGENETICS INC [US]) 19 November 1998 (1998-11-19) cited in the application page 8, lines 26-27 page 7, lines 8-9; claim 1 -----	1-12
Y	IAVAZZO ET AL: "Hyaluronic Acid: An Effective Alternative Treatment of Interstitial Cystitis, Recurrent Urinary Tract Infections, and Hemorrhagic Cystitis?", EUROPEAN UROLOGY, ELSEVIER BV, NL, vol. 51, no. 6, 26 April 2007 (2007-04-26) , pages 1534-1541, XP022048262, ISSN: 0302-2838, DOI: 10.1016/J.EURURO.2007.03.020 the whole document -----	1-12
Y	MAGNUS FALL ET AL: "Bladder Pain Syndrome, Interstitial Cystitis, Painful Bladder Syndrome, and Hypersensitive Bladder Syndrome: New Nomenclature/New Guidelines", CURRENT BLADDER DYSFUNCTION REPORTS, CURRENT SCIENCE INC, NEW YORK, vol. 6, no. 3, 7 July 2011 (2011-07-07), pages 116-127, XP019941228, ISSN: 1931-7220, DOI: 10.1007/S11884-011-0098-3 the whole document see esp. Tables 4 and 5 and Fig. 2 -----	1-12
Y	JEMAN RYU ET AL: "Elimination of Hunner's Ulcers by Fulguration in Patients With Interstitial Cystitis: Is It Effective and Long Lasting?", KOREAN JOURNAL OF UROLOGY, vol. 54, no. 11, 1 January 2013 (2013-01-01), page 767, XP055227502, ISSN: 2005-6737, DOI: 10.4111/kju.2013.54.11.767 the whole document -----	3
A	DATABASE EMBASE [Online] ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; July 2006 (2006-07), TAKEI M ET AL: "Dealing with interstitial cystitis", XP002750826, Database accession no. EMB-2006381195 abstract -/--	1-12

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2016/065975

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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