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(54) Titre : RABEXIMOD DANS LE TRAITEMENT DE LA POLYARTHRITE RHUMATOIDE
(54) Title: RABEXIMOD IN THE TREATMENT OF RHEUMATOID ARTHRITIS

(57) Abrégé/Abstract:

The present invention relates to therapeutic uses of compositions comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3- b]quinoxaline in the treatment of human subjects suffering from Rheumatoid Arthritis.



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Abstract:

The present invention relates to therapeutic uses of compositions comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline in the treatment of human subjects suffering from Rheumatoid Arthritis.

RABEXIMOD IN THE TREATMENT OF RHEUMATOID ARTHRITIS

Technical field

5 The present invention relates to therapeutic uses of compositions comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline (rabeximod) in the treatment of rheumatoid arthritis. The present invention further relates to oral composition comprising a crystalline form of 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline (rabeximod) that are particularly suitable for use in these treatments.

Background Art

 The compound rabeximod has been described in European patent application publication EP1756111A1 and its US counterpart US 2005/288296. The preparation
15 of rabeximod is specifically described in these patent publications, as compound E. The process described is a small-scale process without any description on how to make a process that can be used for GMP and up scaled. The compound rabeximod was not isolated as a solid.

 EP1756111 and US 2005/288296 describe initial tests of rabeximod (com-
20 pound E) in animal models for rheumatoid arthritis and multiple sclerosis.

 The objective of the present invention is to provide efficacious treatments of subjects suffering from rheumatoid arthritis. A further objective of the present invention is to provide formulations that can suitably be used to administer therapeutically effective dosages of rabeximod in these (and other) methods of treatment.

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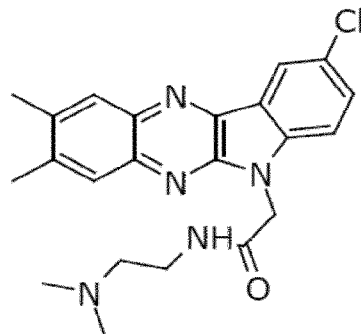
Summary of the Invention

 The invention, generally stated, concerns new and improved formulations containing rabeximod or a salt thereof as well as new treatments and dosage regimens using rabeximod in the rheumatoid arthritis therapeutic area.

30 Specific objects and advantages of these formulations, treatments and dosage regimens will appear from the following description, and claims.

Description of the invention

The compound known under the INN 'rabeximod' has the IUPAC name 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethoxy)-6H-indolo-[2,3-b]quinoxaline and has the following molecular structure..



The preparation of Rabeximod is described in EP1756111A1 and US2005/288296. Throughout the present application, the terms "Rabeximod", "rabeximod" and "9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethoxy)-6H-indolo-[2,3-b]quinoxaline" are used interchangeably and mean the compound in any solid form or liquid form unless otherwise indicated or implied under the given circumstances.

Compositions

In a first aspect the present invention relates to a solid oral composition comprising a crystalline form of 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethoxy)-6H-indolo-[2,3-b]quinoxaline (Rabeximod) or a pharmaceutically acceptable salt thereof and optionally a pharmaceutically acceptable additive.

The pharmaceutically acceptable additive is typically present and is selected from one or more of a filler, glidant, and lubricant, as long as the additive do not affect stability of the rabeximod. Typical filler is Microcrystalline cellulose (Avicel PH-102) or (Avicel PH-200). Typical glidant is Silica colloidal anhydrous (Aerosil 200). Typical lubricant is Magnesium stearate.

In a further embodiment rabeximod is a crystalline free base. Preferably, the rabeximod is a crystalline free base having a melting point of 259-261 °C.

In a still further embodiment the composition comprises rabeximod in the form of a dry powder, e.g. a micronized powder. The particle size distribution can be deter-

mined by means of laser diffractometry. In a preferred embodiment, a Malvern Instruments Mastersizer is used to determine the particle size distribution. Using a Malvern Mastersizer apparatus, volume-based size distribution parameters will typically be reported, e.g. in the form of the D10, D50 and D90 values. The average particle size (D50-value), which is also denoted D50-value of the integral volume distribution, is defined in the context of this invention as the particle diameter at which 50 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D50-value. Likewise, 50 percent by volume of the particles have a larger diameter than the D50-value. Analogously, the D90-value of the integral volume distribution is defined as the particle diameter at which 90 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D90-value. Correspondingly, the D10-value of the integral volume distribution is defined as the particle diameter at which 10 percent by volume of the particles have a smaller diameter than the diameter which corresponds to the D10-value. Typically, the rabeximod dry powder has a particle size characterized by a D10 within the range of 0.5-1.0 μm , a D50 within the range of 1.5-3.5 μm , and/or a D90 within the range of 5.5-9.9 μm , when measured using laser light diffractometry.

In accordance with the various aspects of the invention, the composition is preferably provided in the form of a unit dosage form. The term 'unit dosage form' refers to a physically discrete unit suitable as a unitary dosage for human subjects, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with any suitable pharmaceutical carrier(s) and/or excipient(s). Exemplary, non-limiting unit dosage forms include a tablet (e.g., a chewable tablet), caplet, capsule (e.g., a hard capsule or a soft capsule), etc. In accordance with the invention, the unit dosage form, is a unit dosage form that is suitable for oral administration. Most preferably, it is a solid unit dosage form, such as a tablet or capsule, most preferably a capsule, such as a standard gelatin capsule, which is filled with a powder as defined herein.

It is preferred that the solid oral composition of the present invention is an immediate release (IR) composition. Even more preferred in the IR composition of the present invention at least 70% of the rabeximod is dissolved within 45 minutes in a mammalian subject, such as a human. More preferred, at least 90% of the rabeximod is dissolved within 45 minutes in a mammalian subject, such as a human. Optimally,

at least 90% of the rabeximod is dissolved within 15 minutes in a mammalian subject, such as a human.

Even more preferred in the IR composition of the present invention at least 70% of the rabeximod is dissolved within 45 minutes in a standardized *in vitro* dissolution test. More preferred, at least 90% of the rabeximod is dissolved within 45 minutes in a standardized *in vitro* dissolution test. Optimally, at least 90% of the rabeximod is dissolved within 15 minutes in a standardized *in vitro* dissolution test. Unless specified otherwise in this document, *in vitro* dissolution testing of the solid oral composition is carried out in a so called USP dissolution apparatus II at a temperature of 37 °C and a rotational speed of the paddle of 50 to 75 RPM. For investigating the release profile, simulated gastric fluid, typically in an amount of 500 to 900 ml, is used, which has the following composition: sodium lauryl sulphate 2.5 g; sodium chloride 2.0 g; 0.01-0.05 N hydrochloric acid in water 1000 ml. Active ingredient concentrations in the dissolution medium can be determined by any suitable analytical method, like ultraviolet absorption or HPLC analysis.

In a further aspect the present invention concerns a solid oral unit dosage form, such as a capsule or tablet as defined herein, comprising rabeximod in an amount of at least at least 1 mg, more preferably at least 2 mg, at least 4 mg, at least 6 mg, at least 8 mg, at least 10 mg, at least 12 mg, at least 13 mg, at least 14 mg, or at least 15 mg and/or in an amount of 500 mg or less, more preferably 250 mg or less, 100 mg or less, 75 mg or less, 50 mg or less, 40 mg or less, 30 mg or less, 25 mg or less or 20 mg or less; or a salt of rabeximod in the equipotent dosage. As used herein, the term "equipotent" means equally potent or equally capable of producing a pharmacologic effect of certain intensity. For example, if the composition comprises a salt of rabeximod the amount of said salt to be administered typically needs to be adjusted to take account of the molecular weight difference between the free base and salt form. It is also common in the art to refer to amounts of a given compound "equivalent" to a specified amount of a reference compound. For instance, in expressing dose amounts in the label and/or product information of authorized medicinal products comprising a salt form of an active compound that can also be used in free base form, it is customary practice to specify the dose of the free base that the dose of the salt is equivalent to. In this context, the term 'equipotent' is deemed synonymous to the term 'equivalent'. In preferred embodiments, a solid oral unit dosage form as defined herein is provided, comprising rabeximod in an amount within the range of 5-25 mg, 10-20

mg, 12-18 mg, 13-17 mg, or 14-16 mg, e.g. in an amount of about 15 mg; or a salt of rabeximod in the equipotent/equivalent amount. In certain preferred embodiments, a solid oral unit dosage form as defined herein is provided, comprising rabeximod in an amount of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg; or a salt of rabeximod at the equipotent/equivalent amount.

In an embodiment the solid oral unit dosage form is a capsule comprising a dosage selected from any one of 6.25mg, 12.5 mg, 15mg, 25 mg, 37.5 mg, or 50 mg. Preferably the capsule comprises a dosage of rabeximod of 15 mg. Any one of these unit dosage form comprising rabeximod may be administered daily to treat rheumatoid arthritis in a human subject, such a solid oral unit dosage form comprising rabeximod in an amount of 15 mg per unit dosage, preferably this is administered once daily.

Methods of Treatment

In a broad aspect, the present invention relates to methods of treating a subject in need thereof, in particular a subject suffering from and/or diagnosed with rheumatoid arthritis, or a related condition, said method comprising administering to said subject, a composition comprising Rabeximod or a pharmaceutically acceptable salt thereof, preferably a solid oral composition as defined herein before.

In preferred embodiments of the invention, the subject to be treated is a human subject, preferably a human subject suffering from rheumatoid arthritis, preferably moderate rheumatoid arthritis, severe rheumatoid arthritis or moderate to severe rheumatoid arthritis.

In an embodiment the subject to be treated is a human subject suffering from rheumatoid arthritis of global functional status class I, II or III, according to the criteria developed by the American College of Rheumatoid Arthritis. In an embodiment the subject to be treated is a human subject suffering from rheumatoid arthritis of global functional status class of II, III or IV, in particular III or IV.

In an embodiment the subject to be treated is a human subject suffering from rheumatoid arthritis and having a Central laboratory C-reactive protein (CRP) level of at least 1.5 mg/dL.

In some preferred embodiments of the invention, the subject is a poor responder or non-responder to other pharmacological therapies, such as treatment with methotrexate. In some embodiments, the subject has undergone methotrexate treatment for a period of at least 5, at least 10, at least 15 or at least 20 weeks, without

showing significant and/or sufficient response to said treatment or without showing any response to said treatment.

In some embodiments, the subject is a human subject that is considered at increased risk of developing rheumatoid arthritis, e.g. because of genetic predisposition. In some embodiments, the subject is a human subject having one or more genetic markers indicative of increased risk of developing rheumatoid arthritis. In some embodiments, the subject is a human subject having a biomarker profile indicative of increased risk of developing rheumatoid arthritis. In certain embodiments, the present methods comprise the step of identifying subjects that are at increased risk of developing rheumatoid arthritis. In certain embodiments, the present methods comprise the step of diagnosing or establishing whether a subject is at increased risk of developing arthritis.

In preferred embodiments, the present method is a method of treating rheumatoid arthritis, delaying the progression of rheumatoid arthritis, stopping or preventing the progression of rheumatoid arthritis, inducing remission of rheumatoid arthritis, delaying the onset of rheumatoid arthritis or preventing the onset of rheumatoid arthritis.

In further preferred embodiments, the present method is a method of treating a symptom of rheumatoid arthritis, delaying the progression of a symptom of rheumatoid arthritis, stopping or preventing the progression of a symptom of rheumatoid arthritis, inducing remission of a symptom of rheumatoid arthritis, delaying the onset of a symptom of rheumatoid arthritis or preventing the onset of a symptom of rheumatoid arthritis. Said symptom is preferably selected from the group consisting of tender, warm and/or swollen joints; joint stiffness, particularly in the morning and after periods of inactivity, and symptoms not involving joints, such as fatigue and symptoms involving any of the skin, eyes, lungs, heart, kidneys, salivary glands, nerve tissue, bone marrow and blood vessels. In particularly preferred embodiments, said symptom is a symptom involving a joint, in particular the joints attaching the fingers to the hand, the joints attaching the toes to the feet, the wrists, the ankles, the elbows, the hips and/or the shoulders.

In a particularly preferred embodiment, the method achieves an ACR20 response. As used herein, the abbreviation 'ACR' refers to the American College of Rheumatology (ACR) core set of disease activity measures. An ACR20 response is defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in 3 of the following core set measures: physician's assessment of disease activity, patient's assessment of disease activity,

patient's assessment of pain, and patient's assessment of physical function, and levels of an acute-phase reactant (either the C-reactive protein [CRP] level or the erythrocyte sedimentation rate [ESR]). In a particularly preferred embodiment, the method achieves an ACR20 response within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a particularly preferred embodiment, the method achieves an ACR50 response. In a particularly preferred embodiment, the method achieves an ACR50 response within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a particularly preferred embodiment, the method achieves an ACR70 response. In a particularly preferred embodiment, the method achieves an ACR70 response within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a particularly preferred embodiment, the method achieves a decrease from baseline in DAS28 score. The DAS28 is a measure of disease activity in rheumatoid arthritis (RA). DAS stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment. In clinical practice a DAS28 score is typically assessed by counting the number of swollen joints (out of the 28), counting the number of tender joints (out of the 28), taking blood to measure the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP), using questionnaires (e.g. the HAQ which assesses function) and/or asking the patient to make a 'global assessment of health' (indicated by marking a 10 cm line between very good and very bad). These results are then fed into a standardized mathematical formula to produce the overall disease activity score. A DAS28 score of greater than 5.1 implies active disease, less than 3.2 low disease activity, and less than 2.6 remission. In a preferred embodiment, the present method achieves a decrease from baseline in DAS28 score of at least 1.0, e.g. at least 1.05, at least 1.1, at least 1.15 or at least 1.2. In a particularly preferred embodiment, the method achieves said reduction within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a particularly preferred embodiment, the method achieves a reduction in the duration of morning stiffness. Said reduction is preferably achieved within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a further particularly preferred embodiment, the method achieves a reduction in mean swollen and tender and swollen joint count 66/68. The 66/68 Joint Count evaluates 66 joints for swelling and 68 joints for tenderness and pain with movement. The total score is composed of points that are based on the presence of pain and/or swelling in a joint. Said reduction is preferably achieved within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a further particularly preferred embodiment, the method achieves a reduction in 28-joint count. The 28-Joint Count is another standardized evaluation of involving examination of swelling of 28 specific joints. Said reduction in 28-joint count is preferably achieved within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

In a further particularly preferred embodiment, the method achieves improvement in one or more of Subject and Physician Global assessments, pain assessed by Visual Analogue Scale (VAS) and self-assessed physical disability (mHAQ). Said improvement is preferably achieved within e.g. 10-24 weeks of treatment, within 12-20 weeks of treatment, or within 14-18 weeks of treatment.

The method of the invention preferably comprises the administration to the subject of a composition comprising rabeximod or a salt thereof, such as a composition as defined herein elsewhere, through the oral (or enteral) route of administration.

In particularly preferred embodiments of the invention, the treatment comprises the repeated oral administration of a composition containing rabeximod or a salt thereof, such as the oral solid composition as defined herein, at a frequency of at least once every two days or at least once every day. In preferred embodiments of the invention, the treatment comprises the oral or enteral administration of a composition containing rabeximod or a salt thereof, such as the oral solid composition as defined herein, every morning.

In particularly preferred embodiments of the invention, the treatment comprises the once daily administration of the composition.

In particularly preferred embodiments of the invention, the method comprises the administration of rabeximod at a daily dosage of at least 1 mg, more preferably at least 2 mg, at least 4 mg, at least 6 mg, at least 8 mg, at least 10 mg, at least 12 mg, at least 13 mg, at least 14 mg, or at least 15 mg; or a salt of rabeximod in the equipotent daily dosage. In accordance with the various aspects of the invention, the method comprises the administration of rabeximod at a daily dosage of 500 mg or less, more

preferably 250 mg or less, 100 mg or less, 75 mg or less, 50 mg or less, 40 mg or less, 30 mg or less, 25 mg or less or 20 mg or less; or a salt of rabeximod in the equipotent dosage. In particularly preferred embodiments of the invention, the method comprises the administration of rabeximod in a daily dosage within the range of 5-25 mg, 10-20
5 mg, 12-18 mg, 13-17 mg, or 14-16 mg, e.g. about 15 mg; or a salt of rabeximod in the equipotent dose. In certain preferred embodiments, the method comprises the administration of rabeximod at a daily dosage of 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 or 20 mg; or a salt of rabeximod at the equipotent daily dosage.

In particularly preferred embodiments of the invention, the method comprises
10 the administration of rabeximod or a salt thereof in a dosage regime resulting in a minimal rabeximod plasma level, at steady-state, within the range of 25-150 ng/ml, preferably within the range of 30-125 ng/ml, or within the range of 40-100 ng/ml. In particularly preferred embodiments of the invention, the method comprises the administration of rabeximod or a salt thereof in a dosage regime resulting in a
15 rabeximod plasma level, at steady-state, that is substantially within the range of 25-150 ng/ml, preferably within the range of 30-125 ng/ml, or within the range of 40-100 ng/ml, throughout the dosing interval. In particularly preferred embodiments of the invention, the method comprises the administration of rabeximod or a salt thereof in a dosage regime resulting in a rabeximod plasma level, at steady-state, that is within the
20 range of 25-150 ng/ml, preferably within the range of 30-125 ng/ml, or within the range of 40-100 ng/ml, throughout the dosing interval.

In particularly preferred embodiments of the invention, the treatment comprises the repeated administration of the composition containing rabeximod or a salt, hydrate or solvate thereof, preferably in accordance with the above-defined regimens, during
25 a period of at least 8 weeks, at least 12 weeks, at least 14 weeks, at least 16 weeks, at least six months, at least nine months, at least one year, at least two years, at least three years, at least 5 years, or at least 10 years. There is no particular upper limit; treatment may be continued for as long as it is deemed beneficial to the subject's overall health and well-being (as can be determined by appropriately qualified
30 healthcare professionals), e.g. for the rest of the subject's life.

In certain preferred embodiments of the invention, the present method comprises treatment with another medicament for treating rheumatoid arthritis. In preferred embodiments, such other medicament is methotrexate, for instance administered orally or parenterally. In certain preferred embodiments, a method as defined herein

is provided, further comprising treatment with methotrexate, preferably comprising the administration of a stable dose of methotrexate, such as a weekly dose of 15-20 mg. The composition comprising rabeximod or a salt thereof, may be administered before, simultaneously or after administration of methotrexate.

5 In further aspects, the present invention relates to a composition comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline (Rabeximod) or a pharmaceutically acceptable salt thereof, preferably an oral solid composition as defined herein, for use in any of the methods as defined here above.

10 In yet further aspects, the present invention relates to the use of a composition comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline (Rabeximod) or a pharmaceutically acceptable salt thereof, preferably an oral solid composition as defined herein, for the manufacture of a medicament for use in any of the methods as defined here above.

15 Definitions / Misc.

Further embodiments of the process are described in the experimental section herein, and each individual process as well as each starting material constitutes embodiments that may form part of embodiments.

20 The term "treatment" and "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. The term is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications, to delay the progression of the disease, disorder or condition, to alleviate or relief the symptoms and complications, and/or to cure or eliminate the disease, disorder or condition as well as to prevent the condition, wherein prevention is to be understood as the management and care of a patient for the purpose of combating the disease, condition, or disorder and includes the administration of the active compounds to prevent the onset of the symptoms or complications. The treatment may either be performed in an acute or in a chronic way. The patient to be treated is preferably a mammal; in particular, a human being, but it may also include animals, such as dogs, cats, cows, sheep and pigs.

30 The term "and/or" as used herein is intended to mean both alternatives as well as each of the alternatives individually. For instance, the expression "xxx and/or yyy"

means “xxx and yyy”; “xxx”; or “yyy”, all three alternatives are subject to individual embodiments.

As used herein “pharmaceutically acceptable additive” is intended without limitation to include carriers, excipients, diluents, adjuvant, colorings, aroma, preservatives etc. that the skilled person would consider using when formulating rabeximod in order to make a pharmaceutical composition.

The adjuvants, diluents, excipients and/or carriers that may be used in the composition of the invention must be pharmaceutically acceptable in the sense of being compatible with rabeximod and the other ingredients of the pharmaceutical composition, and not deleterious to the recipient thereof. It is preferred that the compositions shall not contain any material that may cause an adverse reaction, such as an allergic reaction. The adjuvants, diluents, excipients and carriers that may be used in the pharmaceutical composition of the invention are well known to a person within the art.

The above embodiments should be seen as referring to any one of the aspects (such as ‘solid oral composition comprising a crystalline form of Rabeximod’ and/or ‘solid oral unit dosage form, such as a capsule or tablet’) described herein as well as any one of the embodiments described herein unless it is specified that an embodiment relates to a certain aspect or aspects of the present invention.

All references, including publications, patent applications and patents, cited herein are hereby incorporated by reference to the same extent as if each reference was individually and specifically indicated to be incorporated by reference and was set forth in its entirety herein.

All headings and sub-headings are used herein for convenience only and should not be construed as limiting the invention in any way.

Any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

The terms “a” and “an” and “the” and similar referents as used in the context of describing the invention are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context.

Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein.

Unless otherwise stated, all exact values provided herein are representative of corresponding approximate values (e.g., all exact exemplary values provided with respect to a particular factor or measurement can be considered to also provide a corresponding approximate measurement, modified by "about," where appropriate).

5 All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context.

The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise indicated. No language in the
10 specification should be construed as indicating any element is essential to the practice of the invention unless as much is explicitly stated.

The citation and incorporation of patent documents herein is done for convenience only and does not reflect any view of the validity, patentability and/or enforceability of such patent documents.

15 The description herein of any aspect or embodiment of the invention using terms such as "comprising", "having", "including" or "containing" with reference to an element or elements is intended to provide support for a similar aspect or embodiment of the invention that "consists of", "consists essentially of", or "substantially comprises" that particular element or elements, unless otherwise stated or clearly contradicted by
20 context (e.g., a composition described herein as comprising a particular element should be understood as also describing a composition consisting of that element, unless otherwise stated or clearly contradicted by context).

This invention includes all modifications and equivalents of the subject matter recited in the aspects or claims presented herein to the maximum extent permitted by
25 applicable law.

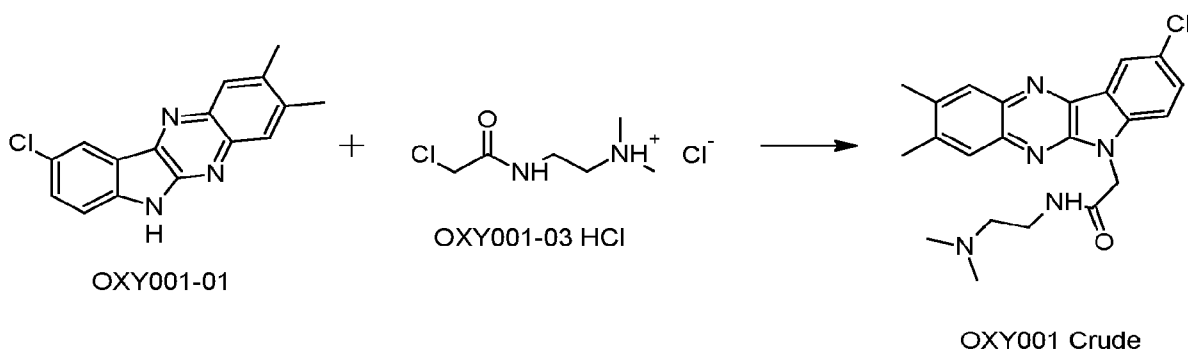
The present invention is further illustrated by the following examples that, however, are not to be construed as limiting the scope of protection. The features disclosed in the foregoing description and in the following examples may, both separately and in any combination thereof, be material for realizing the invention in diverse forms
30 thereof.

Brief Description of the Drawings

Figure 1: Mean plasma concentrations of Rabeximod (ng/mL) in patents with moderate and severe rheumatoid arthritis following repeated once daily oral administration of Rabeximod (in combination with a atable dose of methotrexate) at week 12.

Experimental

Process for making Rabeximod.



The Starting materials: OXY001-01 has CAS number 49764-31-0 and OXY001-03 HCl has CAS number 4584-46-7.

Starting materials: OXY001-01 and OXY001-03 HCl

Table A: Overview Required Raw Materials and Quantities

Item Description	MW	Mol	Quantity re-quired	Eq.
OXY001-01	281.74	46.3	13.0 kg	1.0
OXY001-03 HCl	201.09	92.5	18.6 kg	2.0 ^a
50% NaOH aq. solution	40.00	370.1	29.6 kg	8.0 ^a
Potassium iodide, KI	166.00	37.5	6.2 kg	0.81 ^a
Tetrahydrofuran, THF	-	-	705 L	54.2 ^c
Potable water	-	-	395 L	30.4 ^c

a) mol//mol of OXY001-01; b) kg/kg of OXY001-01; c) L/kg of OXY001-01

Table B: Raw/Intermediate Materials Specifications

Item Description	Parameter	Method	Specification
OXY001-01	Appearance	Visual	Yellow to orange/brown solid
	ID	NMR	Conforms to structure
	Purity	HPLC	≥ 80%
	Use test	HPLC	≥ 98% of OXY001
OXY001-03 HCl	Appearance	Visual	White to off-white solid
	ID	NMR	Conforms to structure
	Residual EtOAc	NMR	To be reported
	Purity	GC	≥ 90%
50% NaOH aq. solution	Appearance	Visual	Colorless liquid
	ID	pH at 25 °C	12-14
	Assay	-	> 31 w/w% from CoA
Potassium iodide, KI	Appearance	Visual	Colorless to white solid
	ID	EP	Conforms
	Assay by titration	-	≥ 95% from CoA
Tetrahydrofuran, THF	Appearance	Visual	Colorless liquid
	ID	NMR	Conforms to reference
	Purity	GC	≥ 99%

Resulting Product: OXY001 Crude (crude rabeximod)

Batch size: 11.38 kg of OXY001 Crude

- 5 **Process description:** OXY001-01 (1.0 equivalent) was dissolved in tetrahydrofuran (15.4 volumes) and 50% NaOH aqueous solution (8.0 equivalents in relation to OXY001-01) in reactor (reactor was running under nitrogen at atmospheric pressure)

and mixed at +55 to +60 °C up to approximately 1 hour until clear dark red solution was formed. Potassium iodide (0.81 equivalents) was added under vigorous stirring and mixed for 10 to 30 minutes at +55 to +60 °C. OXY001-03 HCl (2.0 equivalents) was added to the solution and mixed for at least 2 hours at +55 to +60 °C. Following completion of the reaction, the mixture was quenched with water (15.4 volumes) and tetrahydrofuran removed (15.4 volumes) by evaporation under reduced pressure. The slurry was cooled to +20 to +25 °C and stirred for 1 hour and filtered with a Nutch filter using Polyamide filter cloth (25 µm) or similar as filter media. Resulting cake was washed 3 times with water (3 x 5 volumes) until the pH of the filtrate was between 8-7 and dried on the filter at +40 to +45 °C for at least 12 hours by air suction and additionally in a vacuum tray dryer for 12 hours at +40 °C. Afterwards resulting material was suspended in tetrahydrofuran (25 volumes) at +45 to +50 °C for at least 1 hour. OXY001 Crude was isolated by filtration with a Nutch filter using Polyamide filter cloth (25 µm) or similar as filter media and washed 2 times on the filter with tetrahydrofuran (2 x 7 volumes). Resulting cake was dried on the filter at +40 to +45 °C for at least 12 hours and additionally in a vacuum tray dryer for 12 hours at +40 °C.

Theoretical yield: 18.96 kg

Yield: 60±5% (11.38±0.95 kg)

Maximum volume: 500 L

Purification of crude Rabeximod:

OXY001 crude (1.0 equivalent) was dissolved in tetrahydrofuran (10 volumes), water (3 volume), and 2M HCl (1.4 volumes) mixture. The solution was clear filtered and heated to +50 °C. pH of mixture was adjusted to 10-12 by addition of 2M NaOH (1.3 volume). The formed slurry was cooled to +20 to +25 °C and diluted with water (12 volumes).

After stirring for at least 12 hours the slurry was filtered at +20 to +25 °C and washed on the filter with tetrahydrofuran:water (5:2) mixture (2x3 volumes). Rabeximod has a molecular weight of 409.92 g/mol and is isolated as a crystalline free base having a melting point of 259-261 °C.

Process Description:

The micronisation operation is performed using a standard jet-mill. The set point for the particle size was that not less than 90% of the particles should be smaller than

10µm. In-process samples were drawn and analyzed using a Malvern Mastersizer during the process to verify that a sufficient size reduction had been achieved (Malvern Mastersizer 2000 instrument, equipped with a Scirocco 2000(A) dispersion unit and a Micro Tray, operated at an air pressure of 2.5 bar, a feed rate of 60%, a measuring time of 5 seconds and a background time of 5 seconds; compliant with Ph.Eur method 2.9.31).

Results of the micronisation step in particle size is provided in Table 1 for Rabeximod drug substance batches.

Table 1: Particle size results following micronisation of Rabeximod drug substance batches

Batch No.	Batch size	Feed particles	Result after micronisation			
			% <10 µm	D(0.1)	D(0.5)	D(0.9)
146-32	20 g	41.9%		0.7 µm	2.2 µm	8.2 µm
149	5902 g	30.9%		0.6 µm	2.0 µm	5.9 µm
153	1015 g	32.7%		0.6 µm	1.9 µm	5.7 µm
262-1 ¹	3430 g	29.0%		0.7 µm	2.2 µm	8.4 µm
262-2 ¹	3640 g	32.6%		0.7 µm	2.2 µm	7.6 µm

¹ The bulk batch was divided into two separate micronisation runs.

Rabeximod Drug Product

The batch formula for the different strengths is depicted in Table 2.

Table 2: Composition Rabeximod Drug Product of the following strengths 6.25, 12.5, 15, 25 or 50 mg

Name of Ingredients	Quantity (mg)					Function	Reference To Standards
	6.25 mg	12.5 mg	15 mg	25 mg ²	50 mg ²		
Active substance							
Rabeximod ¹	6.25	12.5	15	25	50	Active substance	In-house specifications

Name of Ingredients	Quantity (mg)					Function	Reference To Standards
	6.25 mg	12.5 mg	15 mg	25 mg ²	50 mg ²		
Excipients							
Microcrystalline cellulose (Avicel PH-102)	211.55	205.3	202.8	-	-	Filler	Ph. Eur.
Microcrystalline cellulose (Avicel PH-200)	-	-		165	140	Filler	Ph. Eur.
Silica colloidal anhydrous (Aerosil 200)	-	-		6	6	Glidant	Ph. Eur.
Magnesium stearate	2.2	2.2	2.2	4	4	Lubricant	Ph. Eur.
Capsule							
Gelatine capsules Size 1 Swedish orange	1 ea	1 ea	1 ea	1 ea	1ea	-	In-house

¹ If the API (rabeximod) purity is lower than 98.0% the master formula unit is corrected accordingly (for API and Microcrystalline Cellulose).

² To improve the flow characteristics for these two high doses the concentrations of the lubricant and magnesium stearate were increased and silica colloidal added.

5

Process description

The required quantity of microcrystalline cellulose was weighed and split into two equal portions. First portion of microcrystalline cellulose followed by the entire amount of Rabeximod drug substance was passed through a nominal 1000 µm screen and transferred directly inside an appropriate sized blending bin having a capacity such that (total) powder fill is between 33% and 66% of blending bin volume. The second portion of microcrystalline cellulose (and silica colloidal if applicable) was

passed through a nominal 1000 µm screen and transferred directly inside the same blending bin. The mixture was blended at appropriate speed and time to make a uniform distribution, such as 17 rotations per minute (RPM) for about 20 min at following room conditions +15 to +25°C and 35 to 65%RH (Relative Humidity). Optional samples were taken after 15 and 20 minutes to assess blend homogeneity. The amount of magnesium stearate was passed through a 700 µm nominal screen into the blending bin. The mixture was blended for at appropriate speed and time to make a uniform distribution, such as 17 RPM for at least 3 min followed by sampling (10 samples: 3 x top, 4 x middle, and 3 x bottom) to determine blend homogeneity (acceptance criteria: average of 10 content samples between 95.0 – 105.0% of label claim with RSD ≤ 5.0%). Blended mixture was transferred to double polyethylene bags in a rigid High Density Poly Ethylene (HDPE) container. Following acceptable blend content homogeneity, the mixture was processing further in a capsule filling equipment at a target weight of 220 mg per capsule (or 200 mg for 25/50 mg strengths). Thereafter from the accepted capsules the required samples were taken for release testing, stability, and retain and subsequently stored in double polyethylene bags in a rigid HDPE plastic container before packaging (current configuration is a blister, previously HDPE bottle).

Current packaging configuration is an appropriate blister pack such as an opaque, white 250 µm Polyvinylchloride (PVC) with 40 grams per square meter (gsm) Polyvinylidene chloride (PVdC) (Duplex) laminate heat sealed to 20 µm aluminium foil. Each blister pack contains multiple capsules such as 18 capsules.

Batch release results of batches used in Phase 2 and Phase 1 clinical studies are provided in Table 3 and Table 4, respectively.

The drug substance is virtually immediately released from the formulation with > 90% released after 45 minutes. During the development of the formulations containing 12.5 mg, 25 mg, and 50 mg for the clinical phase study it was shown that for all three strengths more than 90 % of the drug substance was already released after 15 minutes. In conclusion the capsules meet the requirements for conventional-release dosage forms in Ph. Eur. and immediate release dosage forms in USP.

Table 3: Batch release results of Rabeximod drug product batches used in Phase 2 clinical study

Capsule Strength Use of Batch		6.25 mg Clinical Phase II	12.5 mg Clinical Phase II	15 mg Clinical Phase II	25 mg Clinical Phase II
Test	Specification	Results			
Appearance	Yellow powder contained in a size 1 Swedish orange hard gelatine capsule	Complies	Complies	Complies	Complies
Assay (High Performance Liquid Chromatography (HPLC))	90.0 – 110.0% of label strength (LS)	101.1%	100.3%	101.9%	99.1%
Identification (HPLC)	The retention time of the main peak in the sample chromatogram corresponds to that of the main peak in the standard chromatogram	Complies	Complies	Complies	Complies
Related Substances (HPLC) Largest impurity Number of impurities > 0.05% w/w	≤ 1.0 % w/w To be reported Relative retention time (RRT)	Complies <u>RRT % w/w</u> 1.16 0.06 1.36 0.08 Total = 0.14 % w/w No impurity >0.1% w/w	Complies <u>RRT % w/w</u> 1.16 0.06 1.35 0.09 Total = 0.15% w/w No impurity >0.1% w/w	Complies <u>RRT % w/w</u> 1.16 0.07 1.36 0.08 Total = 0.15% w/w No impurity >0.1% w/w	Complies <u>RRT % w/w</u> 1.16 0.07 1.35 0.09 Total = 0.16% w/w No impurity >0.1% w/w
Sum of impurities >0.1% w/w	≤ 2.0 % w/w				
Dissolution	Not less than 70 % @ 45 mins	96.6%	99.3%	98.7%	97.2%

Content Uniformity					
Stage 1 acceptance value (AV)	$\leq L1$ (15.0)	AV ₍₁₀₎ = 5.1	AV ₍₁₀₎ : 1.6	AV ₍₁₀₎ = 1.9	AV ₍₁₀₎ : 4.3
Stage 2 acceptance value (AV)	$\leq L2$ (25.0) and no individual content for Rabeximod in the dosage unit is less than (1-L2 x 0.01)M nor more than (1+ L2 x 0.01)M				
Microbial Limit Test	Total bacteria not more than 1000 Colony Forming Unit (CFU)/g.	25 CFU/g	<10 CFU/g	< 10 CFU/g.	<10 CFU/g
Total Viable Aerobic Count	Total fungi not more than 100 CFU/g	10 CFU/g	< 10 CFU/g	< 10 CFU/g	< 10 CFU/g
Absence of <i>Escherichia-coli</i>	Absence of <i>Escherichia-coli</i> confirmed	Absence confirmed	Absence confirmed	Absence confirmed	Absence confirmed

Table 4: Batch release results of batches used in Phase 1 clinical study

Capsule Strength		12.5 mg	50 mg
Use of Batch		Clinical Phase 1	Clinical Phase 1
Test	Specification		
Appearance	White/opaque white gelatine capsule containing yellow powder	Complies	Complies
Assay (HPLC)	90.0 – 110.0% of LS	98.5%	96.2%
Identification (HPLC)	Conforms to standard chromatogram	Complies	Complies

Capsule Strength Use of Batch		12.5 mg Clinical Phase 1		50 mg Clinical Phase 1	
Test	Specification				
Related Substances (HPLC)	Read and record	<u>RRT</u>	<u>% w/w</u>	<u>RRT</u>	<u>% w/w</u>
		0.85	0.05	0.85	0.05
		0.91	0.10	0.90	0.09
		0.92	< LOQ ¹	0.92	< LOQ
		0.93	0.05	0.94	0.05
		0.97	< LOQ	0.97	< LOQ
		1.09	< LOQ	1.08	< LOQ
		1.11	0.06	1.11	0.07
		Total	0.26	Total	0.26
Dissolution (HPLC)	NLT 70% of label strength @ 45 min	98.0% @ 45 min		97.0% @ 45 min	
Content Uniformity (HPLC)	85 – 115% of label strength [%RSD ≤ 6%]	97.5% [%RSD ₁₀ = 2.8%]		95.2% [%RSD ₁₀ = 2.1%]	

¹ Limit of Quantification

Phase 1 clinical trial

The Phase 1 study assessed the safety, tolerability, pharmacokinetics and pharmacodynamics of single and multiple oral rising doses of Rabeximod (in a capsule formulation) in healthy male volunteers. The study also included an open-label, randomised, two-period crossover part that was designed to investigate the effect of food on the pharmacokinetics of Rabeximod. In total, 87 healthy male subjects were enrolled into the study.

Results demonstrated that Rabeximod was well tolerated at single doses up to 400 mg. Multiple oral doses up to a 200 mg loading dose followed by 50 mg maintenance dose were also well tolerated. Higher doses: single dose of 600 mg, and multiple dose of 600 mg loading followed by 100 mg, were less well tolerated due to phototoxicity reactions

Phase II clinical trial

The Phase II study was a randomised, parallel-group, double-blind, dose-ranging, placebo-controlled study of Rabeximod in patients with moderate or severe active RA with an inadequate response to methotrexate. The aim of the study was to evaluate the efficacy and safety of Rabeximod administered at doses of 6.25, 15 and 37.25 mg orally once daily for 12 weeks in combination with methotrexate.

Study Objectives

The primary objective of this study was to evaluate the efficacy (American College of Rheumatology 20) of Rabeximod administered orally once daily for 12 weeks in combination with a stable dose of methotrexate in patients with moderate or severe active rheumatoid arthritis. Efficacy was evaluated by American College of Rheumatology 20 (66/68 joint count) after 12 weeks of treatment.

Secondary objectives were to:

- Evaluate additional efficacy parameters of Rabeximod after 4, 8 and 12 weeks of treatment.
- Evaluate the safety of Rabeximod administered orally once daily for 12 weeks in combination with a stable dose of methotrexate in patients with moderate or severe active rheumatoid arthritis.

- Evaluate patient functional disability status using the modified Health Assessment Questionnaire.
- Evaluate the pharmacokinetics of Rabeximod when administered with a stable dose of methotrexate.
- 5 • Evaluate correlation between plasma concentration and effect at Week 12.
- Evaluate the pharmacodynamic effect of Rabeximod when administered with a stable dose of methotrexate.

The primary endpoint of this study is the American College of Rheumatology (ACR20) 20 improvement measured after 12 weeks of treatment with study drug. The ACR20 is a composite score defined as an improvement of 20% in the number of swollen and tender joints and a 20% improvement in 3 of the following 5:

- Patient self-assessed disability by modified Health Assessment Questionnaire (mHAQ)
- 15 • Physician Global assessment
- Subject Global assessment
- Patient pain assessment
- Acute phase reactant (C-reactive protein [CRP])

20 Secondary efficacy endpoints were as follows:

- ACR20 improvement measured after 4 and 8 weeks of treatment
- Subgroup analysis of ACR20 results from patients enrolled with baseline CRP >1.5 mg/dL.
- ACR50/70 improvement measured after 4, 8 and 12 weeks
- 25 • Original Disease Activity Score (DAS) change from baseline (according to the European League Against Rheumatism [EULAR] Response Criteria). Note: the Original DAS was replaced with DAS28
- Change from baseline in: number of swollen/tender joints, morning stiffness duration. Subject and Physician Global assessments, pain assessed by Visual Analogue Scale (VAS), self-assessed physical disability (mHAQ), erythrocyte sedimentation rate (ESR) and CRP
- 30

- The evaluation of pharmacokinetic (PK) and pharmacodynamic (PD) high sensitive CRP, TNF- α , interleukin-6 [IL-6] and anti-cyclic citrullinated peptide antibody [anti-CCP]) over time

5 Study Design

This was a multicentre, multinational, dose-ranging, randomised, double-blind, multiple dose, placebo-controlled, parallel-group study of Rabeximod administered orally in a total of 225 enrolled patients with moderate or severe active RA. All patients must have been receiving weekly methotrexate treatment for at least 16 weeks (with unchanged doses for at least 8 weeks) up to Day 0 of study.

Diagnosis of RA was based on the American Rheumatism Association (ARA) 1987 revised criteria, having an ACR global functional class of 1 to 3, stable methotrexate dose of at least 15 mg per week and central laboratory CRP level at study entry of at least 1.5 mg/dL and clinical findings of active disease (at least 6 swollen and 6 tender joints to palpation). Individual patient duration in the study was approximately 126 days (a 14-day screening period, an 84-day treatment period [12 weeks], and a 28 day [4-week] follow-up period).

After meeting the inclusion and exclusion criteria and providing informed consent, patients were randomly assigned (1:1:1:1 ratio) to receive 1 of the following treatments:

- 6.25 mg Rabeximod
- 15 mg Rabeximod
- 37.5 mg Rabeximod
- Placebo

A total of 9 visits occurred over the course of the study (screening, randomisation [Day 0, baseline]. Day 1, and Weeks 2, 4, 6, 8, 12 and 16). The Day 1 visit was included for a subgroup of 36 patients (PK/PD subgroup) who were selected at specified study centres to also participate in the PK/PD aspect of the study. Individual patient duration in the study was approximately 126 days (a 14 day screening period, an 84 day treatment period [12 weeks], and a 28 day [4 week] follow-up period).

Efficacy assessments included swollen and tender joint counts (66/68 joint count), morning stiffness, Subject and Physician Global assessments, pain assessments, self-assessed physical disability, ESR, CRP measurements, and the mHAQ.

Safety assessments included AEs, vital signs, weight, physical examination, 12-lead ECG and safety laboratory tests (serum chemistry, haematology and urinalysis).

In addition to standard efficacy and safety assessments, it was planned that 40 patients in selected study centres would have blood draws at the beginning of the study (Day 1) and at the end of the study (Week 12) to assess the PK of Rabeximod. The actual number of patients who participated in the PK aspect of the study was 36. The ACR20, ACR50 and ACR70 are assessments of RA improvement. The mHAQ is a validated instrument used to assess patient satisfaction in activity of daily living. It was planned to use the Original DAS as the outcome measure, but this was replaced with DAS28 because it is used more frequently in therapeutic studies have been used in many RA studies.

Study Population

Male or female patients who met all of the following criteria were eligible for participation in the study:

1. >18 years old.
2. Diagnosed with RA based on the ARA 1987 revised criteria at least 16 weeks prior to study enrolment. Day 0.
3. An ACR global functional status class of 1 to 3.
4. Active disease, defined as the presence of 6 swollen joints and 6 tender joints in a 44 joint examination.
5. C-reactive protein level at screening of 1.5 mg/dL.
6. Had been taking oral or parenteral methotrexate (15 mg weekly or above), had been using methotrexate for at least 16 weeks (up to Day 0), and had been on a stable dose for at least 8 weeks, up to Day 0 (patients using 10 to 15 mg methotrexate may have been considered for inclusion if an unacceptable toxicity was recorded when higher doses were used).
7. Stable optional RA medication:
 - a. Folic acid supplementation if already in use
 - b. Nonsteroidal anti-inflammatory drugs including cyclooxygenase-2 (Cox-2) inhibitors - doses must have been stable for 4 weeks prior study enrolment (Day 0) with study drug and consistent with labelling recommendations

- c. Acetylsalicylic acid was allowed in low doses as cardiovascular prophylaxis
 - d. Oral glucocorticoids; daily doses of up to 10 mg (inclusive) of prednisolone or equivalent for 4 weeks prior study enrolment (Day 0) with study drug
 - e. Painkillers (acetaminophen, Tramadol and similar, alone or in combinations) usage as per routine instructions was allowed, except for 24 hours before rheumatology evaluations.
8. Where using adequate forms of birth control - defined as 2 methods of birth control (e.g., contraceptive pill and single-barrier method). Birth control was not necessary in patients who has been postmenopausal for > 1 year or who were surgically sterile (including hysterectomy).
 9. Patients must have been able to give informed consent after reading and understanding the patient information sheet, and willing to comply with *all* study procedures including completing all questionnaires.

Patients who met any of the following criteria were not included in the study:

1. Arthritis onset prior to 16 years old.
2. Any of the following infections:
 - a. Known or acute infection that may have affected CRP levels
 - b. Active tuberculosis
 - c. Known chronic infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis B virus (HBV) including positive serology.
3. Ongoing systemic inflammatory condition which may have interfered with the results of clinical or laboratory tests planned in the study (e.g., systemic lupus erythematosus or any other systemic rheumatic disease other than RA).
4. Any clinically significant concurrent medical condition resulting in the following abnormal laboratory values:
 - a. Hepatic
 - i. Aspartate aminotransferase (AST) > 2 x the upper limit of normal (ULN)
 - ii. Alanine aminotransferase (ALT) > 2 x ULN

- iii. Alkaline phosphatase $> 2.5 \times \text{ULN}$
 - iv. Total bilirubin $> \text{ULN}$.
 - b. Renal
 - i. Serum creatinine $> 1.5 \times \text{ULN}$
 - ii. Urea $> 1.5 \times \text{ULN}$
 - iii. Significant proteinuria (2+ on urinary dipstick test).
 - c. Haematology
 - i. Haemoglobin (HGB) $< 9 \text{ g/dL}$
 - ii. Leukocytes $< 3.5 \times 10^9/\text{dL}$
 - iii. Absolute neutrophil count (ANC) $< 1.5 \times 10^9/\text{L}$
 - iv. Platelets $< 100 \times 10^9/\text{L}$.
- 5. Present or previous malignancies, except history of cured squamous or basal skin cell carcinoma.
- 6. Uncontrolled diabetes mellitus.
- 7. Any medical condition, which in the judgment of the Investigator, put the patient at an unacceptable risk by participating in the study.
- 8. Required 1 or several of the following medications:
 - a. Narcotics (except for Tramadol) or any drug for treatment of RA other than NSAIDs, Cox-2 inhibitors, acetaminophen/paracetamol for pain and arthritis control, or aspirin (except for cardiovascular prophylaxis)
 - b. Current or previous use of biological anti-inflammatory or immunomodulatory therapy for treatment of RA (e.g., anti-IL-1 and anti-B-cell treatment)
 - c. Current or previous use of DMARDs (e.g., sulphasalazine, antimalarials, etc.), except methotrexate, within 4 months prior to study enrolment (Day 0)
 - d. Anti-tumour necrosis factor [anti-TNF] 2 months prior to study enrolment (Day 0)
 - e. Intra-articular, intramuscular (i.m.), or intravenous (i.v.) glucocorticoids within 4 weeks prior to study enrolment (Day 0).
- 9. Participation in an investigational study within the past 30 days or expected to be treated with an investigational product during this study period.

10. Current or recent history (within 12 months of screening) of drug or substance abuse, including alcohol.
11. Females who were pregnant or nursing.
12. Any clinically significant abnormality on physical examination, laboratory testing, vital signs, or 12-lead ECG suggestive of a significant unstable medical condition.
13. Any other condition that, in the opinion of the Investigator, could have interfered with the patient's study participation.

10 Test Drug Formulation

Rabeximod was supplied as size 1, Swedish orange gelatine capsules, in microcrystalline cellulose and magnesium stearate, which were produced according to the process described here above. Placebo was supplied as size 1, Swedish orange gelatine capsules, in microcrystalline cellulose and magnesium stearate, with no active ingredient Rabeximod. Placebo capsules were identical in appearance to the test drug formulation. Capsules for all treatment arms were supplied in blisters of identical appearance.

Selection and timing of Dose for Each Patient

The selection of dose for each patient (6.25 mg Rabeximod, 15 mg Rabeximod, 37.5 mg Rabeximod or placebo) was determined by random assignment. The study drug was to be taken at approximately the same time every morning, starting from Day 1. For the PK/PD subgroup, on the day when the PK/PD sampling was scheduled, study drug was to be taken after the first blood sampling. The study design of the treatment phase was double-blind. All study drug, including placebo, were identical in size, shape, colour and taste, thus allowing double-blind conditions to be maintained. All study personnel and patients remained blinded to the drug treatment assignments. Patients self-administered all doses of study drug and were instructed to return all residual, unused and empty packaging to the clinic at scheduled visits. If dosing compliance was not maintained at between 80% and 120% then the patient was to be withdrawn from the study. Patients in the PK/PD subgroup were to take study drug at the clinic on Day 1 and at Week 12. Compliance was monitored through drug accountability. The Investigator, or designee, maintained an inventory record of

study drug received, dispensed, administered and returned to assure the Sponsor that study drug was not dispensed to any person who was not a patient under the terms and conditions set forth in the protocol. Clinically significant protocol deviations were identified based on criteria determined by the project leader to be clinically relevant. Deviations were reported on the CRFs. Additionally, upon completion of the study, certain deviations (e.g., visit window deviations) were identified through the use of SAS® programming.

Pharmacokinetics

The PK assessment of Rabeximod was performed in a subgroup of 36 patients during the study.

Concentration-time profiles for plasma Rabeximod following single (Day 1) and repeated administration (Week 12) of Rabeximod were determined. Results are summarized in the following Table 5.

Table 5: Summary of Pharmacokinetic Parameters by Visit (PK Population)

	6.35 mg (N=9) ²	15 mg (N=11)	37.5 mg (N=8)
C_{max} (µg/mL)			
Day 1, n	8	10	8
Median	7.05	16.0	41.8
Min, Max	4.41, 21.8	12.5, 37.5	25.3, 66.3
Geometric mean ¹	7.92	18.3	41.7
Week 12, n	7	11	4
Median	37.5	91.6	238.0
Min, Max	11.0, 95.1	44.3, 134	140.0, 314.0
Geometric mean ¹	31.0	79.7	218.0
T_{max} (hours)			
Day 1, n	8	10	8
Median	8.03	6.04	5.03
Min, Max	5.92, 24.0	1.98, 24.0	2.0, 8.0
Week 12, n	7	11	4
Median	2.17	4.0	3.99
Min, Max	0.0, 48.1	0.0, 12.0	3.95, 4.08
AUC_{0-t} (hr*ng/mL)			
Week 12, n	7	11	4
Median	2810.0	5590.0	17500.0
Min, Max	631.0, 10100.0	2140.0, 10300.0	8460.0, 25400.0
Geometric mean ¹	2530	4970.0	15900.0
AUC_{0-τ} (hr*ng/mL)			
Day 1³, n	8	10	9

	Median	107.0	254.0	697.0
	Min, Max	77.3, 197.0	161.0, 547.0	374.0, 1070.0
	Geometric mean ¹	112.0	282.0	689.0
	Week 12, n	7	7	4
	Median	710.0	1480.0	4540.0
	Min, Max	178.0, 2090.0	795.0, 2530.0	2230.0, 5990.0
	Geometric mean ¹	587.0	1530.0	4040.0
	T_{1/2} (hours)			
	Week 12, n	7	11	4
	Median	86.6	77.6	107.0
	Min, Max	49.4, 199.0	37.1, 154.0	83.5, 154.0
	Geometric mean ¹	81.5	77.1	111.0
MTX: methotrexate; C _{max} : maximum observed plasma concentration; SD: standard deviation; T _{max} : time of occurrence of C _{max} ; AUC _{0-T} : area under the concentration versus time curve within a dosing interval; AUC _{0-t} : area under the concentration versus time curve to the last measurable time point; T _{1/2} : apparent terminal half-life; min: minimum; max: maximum ¹ Geometric coefficient of variation = (sqrt(exp(SDln ²)-1))*100 ² Patient 21-018 was mistakenly thought to have received placebo; samples were not analysed for Rob 803 as a result. ³ AUC _{0-T} is equivalent to AUC _{0-t} on Day 1.				

Following a single administration of Rabeximod at 6.25, 15 and 37.5 mg in combination with a stable dose of methotrexate, C_{max} of Rabeximod were attained (T_{max}) at approximately 5 to 8 hours post-dose across all dose levels (median estimates). However, following repeated administration during Week 12, C_{max} was attained earlier at approximately 2 to 4 h post-dose (median estimates). Plasma concentrations of Rabeximod declined during Week 12 (Figure 1) with geometric mean apparent terminal half-lives (t_{1/2}) of 81.5, 77.1 and 111 hours following administration at Rabeximod 6.25, 15 and 37.5 mg, respectively.

Rabeximod terminal half-lives were 81.5, 77.1 and 111 hours following administration at 6.25, 15 and 37.5 mg, respectively. The observed geometric mean values for AUC_{0-T}, AUC_{0-t} and C_{max}, increased in an approximately dose-proportional manner over the dose range of 6.25 to 37.5 mg when administered in combination with a stable dose of methotrexate.

Methotrexate does not appear to have an impact on the kinetics of Rabeximod.

Efficacy

An assessment of tender and swollen joints was performed for the ACR response criteria. Joints to be evaluated for disease activity assessment (using the ACR 66/68 joint count) included the following: temporomandibular, sternoclavicular, acromioclavicular, shoulder, elbow, wrist, all 5 metacarpophalangeal joints, 4 proximal interphalangeal joints, 4 distal interphalangeal, thumb interphalangeal joint, hip (for tenderness only), knee, ankle, tarsus, 5 metatarsophalangeal, 4 proximal interphalangeal and foot thumb interphalangeal joints at each side. In accordance with the protocol, an independent joint reviewer performed the rheumatology examination, where possible. If an independent joint reviewer was not available, the same examiner performed all rheumatology examinations for a patient throughout the study.

Patient satisfaction in performing activities of daily living was assessed using the mHAQ. The mHAQ included questions concerning the perceived patient satisfaction in various activities of daily living: arising, dressing and grooming, eating, walking, hygiene, reach, grip and 3 specific daily activities (run errands, get in and out of car, do chores). Also, aids or devices used and help from another person needed to perform any of the activities were captured. Patients rated activities by difficulty level, ranging from the ability to complete the activity 'without any difficulty' to 'unable to perform' a specific activity. Higher numbers indicated more difficulty performing the activities. Patient self-assessed physical disability was calculated as Disability Index (DI).

Physician Global assessment of overall disease activity occurred as presented in the schedule of events (Table 1). Physicians assessed each patient's overall disease activity by making a mark on a 100 mm VAS. The low end of the scale indicated 'no symptoms' and the high end indicated 'very severe'. Physicians were asked to mark the VAS based on the following instruction: "Make a mark on the line indicating your assessment of the patient's overall disease activity." This assessment was completed after the joint assessment.

Subject Global assessment of the impact of their arthritis occurred as presented in the schedule of events (Table 1). Patients assessed the impact their Arthritis by making a mark on a 100 mm VAS. The low end of the scale indicated 'no impact' and the high end indicated 'very significant impact.' Patients were asked to

mark the VAS according to the following question: "Considering all of the ways your arthritis affects you, mark 'x' on the scale for how well you are doing". This VAS value was also used for the calculation of DAS28 and ACR20/50/70.

5 Patient pain assessment occurred as presented in the schedule of events (Table 1). Patients assessed the pain associated with their Arthritis by making a mark on a 100 mm VAS. The low end of the scale indicated 'no pain' and the high end indicated 'very severe pain'. Patients were asked to mark the VAS based on the following question: "How much pain have you had because of your illness in the past week."

10 Blood was drawn to evaluate ESR and CRP as presented in the schedule of events (Table 1). An ESR tube containing anticoagulated blood was placed upright in a tube, for-purpose rack. C-reactive protein was measured by the central laboratory using high sensitivity methodology.

15 The Original DAS was to be assessed as presented in the schedule of events (Table 1); further information on Original DAS is provided in the Protocol. However, as DAS28 is a more frequently used outcome measure in therapeutic studies. Original DAS was replaced with DAS28. The DAS28-ESR was based on an external standard of RA disease activity and combined information from a swollen/tender 28 joint count, ESR, and a general health (GH) assessment on a VAS. For the 28 joint
20 count, the following joints were assessed: shoulders, elbows, wrists, metacarpophalangeal joints, proximal interphalangeal joints, and the knees, at each side. In addition, the patient's GH measured on a VAS of 100 mm (both are useable for this purpose) was obtained. The DAS28 had a continuous scale ranging from 0 to 10. The level of disease activity could be interpreted as low ($\text{DAS28} < 3.2$), moderate ($3.2 < \text{DAS28} < 5.1$) or high ($\text{DAS28} > 5.1$). A patient was considered to be in remission if
25 they have a DAS28 lower than 2.6.

Morning stiffness was assessed by having the patient answer the following question: "On average, how long does it take for your morning stiffness to resolve?" The answer was recorded in minutes.

30 Patients who received Rabeximod (plus methotrexate) experienced a greater improvement in symptoms with onset starting at least 8-12 weeks after the first dose, with further improvement noted during follow-up (Week 16) compared with patients who received placebo (plus methotrexate). At week 12, a larger proportion of patients

in the Rabeximod groups achieved ACR20 compared with patients in the placebo group. The proportions of patients achieving ACR20 in the Rabeximod groups continued to increase at Week 16, with the best results in the Rabeximod 15 mg group.

5 Similar results were observed for ACR50. At Week a higher percentage of patients in the Rabeximod 6.25,15, and 37.5 mg groups achieved an ACR50 response, respectively, compared with the placebo group, with the best results in the Rabeximod 15 mg group. The increases in the proportions of patients achieving ACR50 were greater at Week 16.

10 DAS28 mean baseline scores for each treatment group was very high, indicating a high disease activity in the study population. For the Rabeximod groups there was a gradual decrease (improvement) in mean DAS28 score from baseline during the study, with better responses observed at Weeks 12 and 16 compared with placebo; at Week 12 changes in mean DAS28 scores were -1.063, -1.214 and -1.204 points in the Rabeximod 6.25, 15 and 37.5 mg groups, respectively, compared with
15 -0.983 point in the placebo group..

The percentage of patients achieving a good or moderate EULAR response rate gradually increased during the study, reaching 37.8, 67.7 and 55.8% in the Rabeximod 6.5,15 and 37.5 mg groups, respectively, compared with 38.5% in the placebo group at Week 16.

20 For the Rabeximod groups, there was a notable decrease (improvement) from baseline in each separate component of the ACR response: the mean swollen and tender and swollen joint count 66/68, Subject and Physician Global assessments of disease activity (VAS), joint pain, HAQ-DI, acute phase reactants (CRP and ESR)..

25 There were greater reductions (improvement) in the duration of morning stiffness for the Rabeximod groups compared with placebo at the majority of time points, with the best results seen in the Rabeximod 15 mg group, especially at week 16.. Percentage mean reduction from baseline in joint pain was notable at week 1, with best results seen in the Rabeximod 15 mg group. At Week 16, notable improvements in percentage mean reduction from baseline in swollen (66) and tender (68) joint
30 counts, Physician and Subject Global assessments of disease activity were observed, with best results seen in the Rabeximod 15 mg group.

Safety

Safety measurements for this study included AEs, clinical laboratory tests, physical examinations, vital signs and resting 12-lead ECGs.

Rabeximod, administered once daily at 6.25, 15 and 37.5 mg was well-tolerated in RA patients taking methotrexate. No deaths occurred during the study. Overall, 96 patients (42.7%) experienced at least 1 TEAE during the study, 65 (28.9%) of whom experienced at least 1 TEAE which was considered related to study drug. The proportion of patients experiencing study drug-related AEs was greater in the Rabeximod groups (34.5%; pooled) than in the placebo group (11.1%), with the majority of these events occurring in the Rabeximod 37.5 mg group (32 patients [58.2%]). Overall, the majority of events were mild or moderate in severity.

The majority of changes in physical examinations that occurred during the study were skin abnormalities, all of which occurred in the Rabeximod group and most of which were reported as AEs. These events clearly demonstrate a dose response as the majority of events were reported in the Rabeximod 37.5 mg group, followed by the Rabeximod 15 mg group and then the Rabeximod 6.25 mg group.

Overall, there were no notable changes in vital signs and 12-lead ECGs over the course of the study.

CLAIMS

1. Composition comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethyl-amino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline (Rabeximod) or a salt thereof, for
5 use in a method of treating a human subject suffering from and/or diagnosed with rheumatoid arthritis, said method comprising the oral administration to said subject, of said composition comprising Rabeximod or a pharmaceutically acceptable salt thereof.

2. The composition for use according to claim 1, wherein the method
10 comprises the administration of rabeximod at a daily dosage within the range of 1-500 mg, or the administration of a salt of rabeximod at the equivalent daily dosage.

3. The composition for use according to any one of claims 1-2, wherein the method comprises the administration of rabeximod at a daily dosage within the range of 5-25 mg, or the administration of a salt of rabeximod at the equivalent daily dosage.

15 4. The composition for use according to any one of the preceding claims, wherein the method comprises the administration of rabeximod or a salt thereof in a dosage regime resulting in a rabeximod plasma level, at steady-state, that is within the range of 25-150 ng/ml throughout the dosing interval

5. The composition for use according to any one of the preceding claims,
20 wherein the composition comprising rabeximod is a solid unit dosage form suitable for oral administration, preferably a filled capsule, comprising rabeximod in micronized form.

6. The composition for use according to any one of the preceding claims, wherein the method is a method of treating rheumatoid arthritis, delaying the pro-
25 gression of rheumatoid arthritis, stopping or preventing the progression of rheumatoid arthritis, inducing remission of rheumatoid arthritis, delaying the onset of rheumatoid arthritis or preventing the onset of rheumatoid arthritis.

7. The composition for use according to any one of the preceding claims, wherein the method is a method of treating a symptom of rheumatoid arthritis, delay-
30 ing the progression of a symptom of rheumatoid arthritis, stopping or preventing the progression of a symptom of rheumatoid arthritis, inducing remission of a symptom of rheumatoid arthritis, delaying the onset of a symptom of rheumatoid arthritis or preventing the onset of a symptom of rheumatoid arthritis

8. The composition for use according to claim 7, wherein the symptom is selected from the group consisting of tender, warm and/or swollen joints; joint stiffness, particularly in the morning and after periods of inactivity

9. The composition for use according to any one of the preceding claims,
5 wherein the subject is a poor responder to treatment with methotrexate.

10. The composition for use according to any one of the preceding claims, wherein the subject to be treated is a human subject suffering from rheumatoid arthritis of global functional status class of II, III or IV, preferably III or IV.

11. The composition for use according to any one of the preceding claims,
10 wherein the method achieves one or more of an ACR20 response, a reduction in the duration of morning stiffness and a reduction in mean swollen and tender and swollen joint count 66/68.

12. The composition for use according to claim 11, wherein the method achieves one or more of an ACR20 response, a reduction in the duration of morning
15 stiffness and a reduction in mean swollen and tender and swollen joint count 66/68, within a period of 14-18 weeks.

13. The composition for use according to any one of the preceding claims, wherein the method comprises the repeated administration of the composition containing rabeximod or a salt thereof, during a period of at least 12 weeks,
20 preferably at least 16 weeks.

14. The composition for use according to any one of the preceding claims, wherein, the method further comprises treatment of the subject with methotrexate.

15. Method of treating a human subject suffering from and/or diagnosed with rheumatoid arthritis, said method comprising the oral administration to said subject,
25 of a composition comprising 9-Chloro-2,3-dimethyl-6-(N,N-dimethylaminoethylamino-2-oxoethyl)-6H-indolo-[2,3-b]quinoxaline (Rabeximod) or a salt thereof.

Figure 1

