



No. 13-115446- -00000-0000

Fecha: 2013-05-08 16:45:58 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Follos: 4



Industria y Comercio

SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE
INVENCIÓN

TITULO: COMPOSICIÓN FARMACÉUTICA, MÉTODOS DE TRATAMIENTO
Y USOS DE LA MISMA

SOLICITANTE: BOEHRINGER INGELHEIM INTERNATIONAL GMBH

DIRECCIÓN: Binger Strasse. 173, 55216 Ingelheim am Rhein
Alemania

APODERADO: CARLOS R. OLARTE

BOGOTÁ 08 de Mayo de 2013

OLARTEMOURE

OLARTE MOURE & AS

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-115446- -00000-0000

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Folios: 4

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD

PATENTE PCT

ENTRADA EN FASE NACIONAL

P2013/000066

SOLICITUD DE:

1

☒

Patente de Invención.

☐

Patente de Modelo de Utilidad.

☐

Capítulo I.

☒

Capítulo II.

2

SOLICITANTE
(71)

Nombre: **BOEHRINGER INGELHEIM
INTERNATIONAL GMBH**

Dirección: Binger Str. 173, 55216 Ingelheim
am Rhein

Nacionalidad o Domicilio: Alemania

Lugar de Constitución: Alemania

Teléfono: _____

Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

REPRESENTANTE
O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: Carrera 5 No. 34-03 Bogotá,
Colombia

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olartemoure.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747Bta
TP 74.295

INVENTOR (ES)
(72)

Nombre: VER PAGINA ADJUNTA.

Dirección: VER PAGINA ADJUNTA.

Nacionalidad o Domicilio: VER PAGINA ADJUNTA.

5

PCT (86)

Solicitud Internacional No. PCT/EP2011/069532 Fecha Noviembre 07, 2011

Publicación Internacional No. WO 2012/062698 A1 Fecha Mayo 18, 2012

6

Título (54) **COMPOSICIÓN FARMACÉUTICA, MÉTODOS DE TRATAMIENTO
Y USOS DE LA MISMA**

Clasificación Internacional (51) A61K31/00; A61K 31/341; A61K38/28; A61P3/10

Prioridad
SI ☒ NO ☐

(33) País de Origen

EP

EP

(32) Fecha

Noviembre 08, 2010

Enero 17, 2011

(31) Número de Solicitud

10190303.7

11151059.0

9

Comprobante de pago No. 13-

Fecha _____

10

ANEXOS

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☒

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso.

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones. Declaración bajo la Regla 4.17 (ii) del PCT.

☒

Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

☐

Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

☐

De ser el caso, certificado de depósito del material biológico.

☐

Arte final 12 x 12.

☐

De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

☐

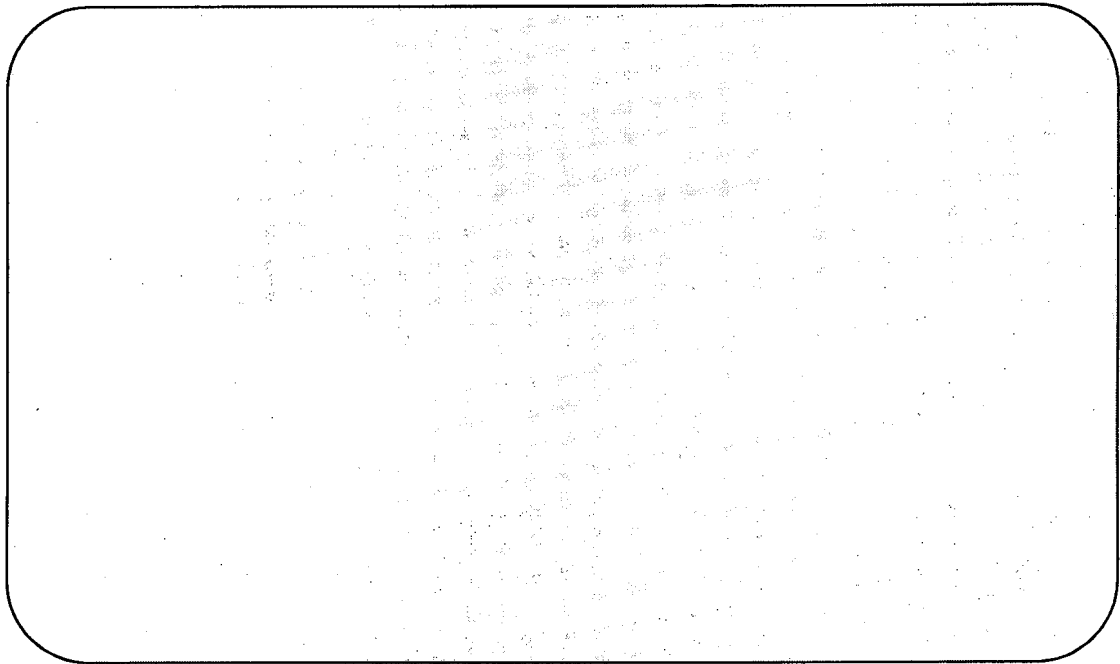
De ser el caso, modificaciones efectuadas a la solicitud internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

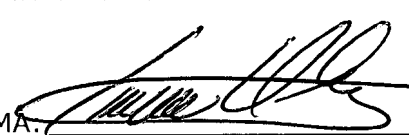


12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA:


C.C. 79.782.747 Btá T.P. 74.295

LISTA DE INVENTORES

PCT/EP2011/069532

Rolf GREMPER

Boehringer Ingelheim GmbH.

Binger Strasse 173

Ingelheim am Rhein 55216

Alemania

Nacionalidad: Alemana

Odd-Erik JOHANSEN

Boehringer Ingelheim GmbH.

Binger Strasse 173

Ingelheim am Rhein 55216

Alemania

Nacionalidad: Noruega

Thomas - KLEIN

Boehringer Ingelheim GmbH.

Binger Strasse 173

Ingelheim am Rhein 55216

Alemania

Nacionalidad: Alemana

Gerd LUIPPOLD

Boehringer Ingelheim GmbH.

Binger Strasse 173

Ingelheim am Rhein 55216

Alemania

Nacionalidad: Alemana

Michael MARK

Boehringer Ingelheim GmbH.

Binger Strasse 173

Ingelheim am Rhein 55216

Alemania

Nacionalidad: Alemana

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -



RECIBO DE CAJA

No. 13 - 0040672

Bogotá D.C., Abril 30 de 2013 - 12:12:26

RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	532438222	29/04/2013	7.078.000.00

*** Conceptos Pagados ***

CANT.	RENTISTICO	CONCEPTO	Vr. UNDITARIO	Vr. CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE INVENCIÓN	500.000.00	500.000.00
				\$500.000.00

SON: **QUINIENTOS MIL PESOS MONEDA CORRIENTE**

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Sede Centro: Carrera 13 No. 27 - 00 Pisos 3,4,5 y 10 Bogotá, D.C.- Colombia

Web: www.sic.gov.co e-mai: info@sic.gov.co Conmutador: (571) 5870000 Fax: (571) 5870284 Línea: 018000-910165 Call Center: (571) 6513240

, Abril 30 de 2013 - 12:12:28



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PATENTE DE INVENCION ☐

MODELO DE UTIL ☐

☐	Indicación que se solicita una patente.
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Descripción de la invención
☐	Dibujos de ser estos pertinentes
☐	Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)
Completa ☐	Incompleta ☐

PATENTE DE INVENCION PCT ☒ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

☒	Indicación que se solicita una PCT
☒	Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
☒	Dibujos de ser estos pertinentes
☒	Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)
Completa ☒	Incompleta ☐

DISEÑO INDUSTRIAL ☐

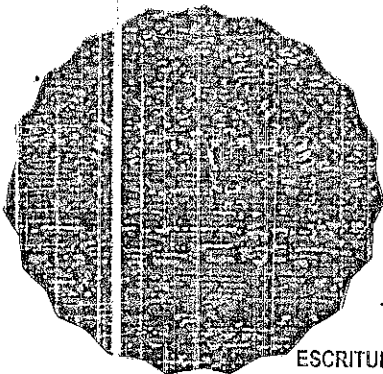
(Art. 119 Decisión 486/00)

☐	Indicación que se solicita Diseño industrial
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐

ESQUEMA DE TRAZADO ☐

(Art. 92 Decisión 486/00)

☐	Indicación que se solicita un esquema de trazado
☐	Datos de identificación del solicitante o de la persona que presenta la solicitud
☐	Representación gráfica de un esquema de trazado
☐	Comprobante de pago de las tasas establecidas
Completa ☐	Incompleta ☐



TESTIMONIO

ESCRITURA: 001416
MINUTA: 000657

K: 007735

DELEGACION DE PODER
QUE OTORGA
BOEHRINGER INGELHEIM INTERNATIONAL GMBH
REPRESENTADO POR
JANNE IVETTE LUQUE CARDENAS
A FAVOR DE
CARLOS REINALDO OLARTE

=====

INTRODUCCION

EN LA CIUDAD DE LIMA AL VEINTISEIS DE JULIO DEL DOS MIL DIEZ, ANTE MI, MARIO GINO BENVENUTO MURGUIA, NOTARIO DE ESTA CAPITAL.

COMPARECEN:

JANNE IVETTE LUQUE CARDENAS, QUIEN MANIFIESTA SER DE NACIONALIDAD: PERUANA, DE ESTADO CIVIL CASADA, DE PROFESION U OCUPACION: ABOGADA Y DOMICILIAR EN AVENIDA REPUBLICA DE PANAMA 3531, OFICINA 1203, DISTRITO DE SAN ISIDRO PROVINCIA Y DEPARTAMENTO DE LIMA, DEBIDAMENTE IDENTIFICADA CON DOCUMENTO NACIONAL DE IDENTIDAD NUMERO 29562321, QUIEN PROCEDE EN REPRESENTACION DE BOEHRINGER INGELHEIM INTERNATIONAL GMBH, CUYAS FACULTADES CONSTAN EN EL PODER OTORGADO CON FECHA QUINCE DE JULIO DEL DOS MIL DIEZ, DEBIDAMENTE LEGALIZADO POR EL MINISTERIO DE RELACIONES EXTERIORES CON FECHA VEINTITRES DE JULIO DEL DOS MIL DIEZ, QUE SE INSERTA, LA COMPARECIENTE ES INTELIGENTE EN EL IDIOMA CASTELLANO, QUIEN SE OBLIGA CON CAPACIDAD, LIBERTAD Y CONOCIMIENTO SUFICIENTE DE CONFORMIDAD CON EL EXAMEN QUE LE HE EFECTUADO DE LO QUE DOY FE; Y ME ENTREGÓ UNA MINUTA QUE ARCHIVO EN SU LEGAJO RESPECTIVO BAJO EL NUMERO DE ORDEN CORRESPONDIENTE Y CUYO TENOR LITERAL ES COMO SIGUE:

MINUTA:

SEÑOR NOTARIO:

SÍRVASE EXTENDER EN SU REGISTRO DE ESCRITURAS PÚBLICAS UNA DE DELEGACION DE PODER QUE OTORGA LA SEÑORA IVETTE LUQUE CARDENAS, IDENTIFICADA CON DNI N° 29562321, DE NACIONALIDAD PERUANA, ESTADO CIVIL CASADA, OCUPACIÓN ABOGADO Y CON DOMICILIO EN AV. REPÚBLICA DE PANAMÁ N° 3531, OFICINA 1203, SAN ISIDRO, QUIEN ACTÚA EN REPRESENTACIÓN DE BOEHRINGER INGELHEIM INTERNATIONAL GMBH, UNA EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE ALEMANIA, CON DOMICILIO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, SEGÚN PODER OTORGADO CON FECHA 13 DE OCTUBRE DE 2009, Y A QUIEN EN ADELANTE SE LE DENOMINARÁ EL PODERDANTE; A FAVOR DEL SEÑOR CARLOS REINALDO OLARTE, IDENTIFICADO CON CÉDULA N° 79.782.747, A QUIEN EN ADELANTE SE LE DENOMINARÁ EL APODERADO; EN LOS SIGUIENTES TÉRMINOS Y CONDICIONES:

PRIMERO: CON FECHA 15 DE JULIO DE 2010, LA EMPRESA BOEHRINGER INGELHEIM INTERNATIONAL GMBH, UNA EMPRESA CONSTITUIDA Y EXISTENTE BAJO LAS LEYES DE ALEMANIA, CON DOMICILIO EN BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, ALEMANIA, OTORGÓ PODER A FAVOR DE EL PODERDANTE, EL CUAL USTED SEÑOR NOTARIO SE SERVIRÁ INSERTAR. ==

SEGUNDO: POR EL PRESENTE DOCUMENTO, EL PODERDANTE DELEGA PODER A FAVOR DE EL APODERADO PARA QUE REPRESENTÉ EN LA REPÚBLICA DE COLOMBIA A LA SOCIEDAD BOEHRINGER INGELHEIM INTERNATIONAL GMBH, TAL COMO CONSTA EN EL PODER ADJUNTO, ANTE CUALQUIER AUTORIDAD ADMINISTRATIVA O JUDICIAL, INCLUYENDO LA SECRETARÍA Y TRIBUNAL DE JUSTICIA DE LA COMUNIDAD ANDINA, PARA EL INICIO, TRAMITACIÓN, OBTENCIÓN, DEFENSA Y HACER RESPETAR TODAS Y CUALQUIERA DE LAS PATENTES DE INVENCION, MODELOS DE UTILIDAD, DISEÑOS INDUSTRIALES, MARCAS, LEMAS COMERCIALES, NOMBRES COMERCIALES, PROTECCIÓN DE DATOS DE PRUEBA, PROTECCIÓN DE SECRETOS EMPRESARIALES, DERECHOS DE AUTOR, REGISTRO DE NOMBRES DE DOMINIO, O SEGUIMIENTO DE PROCEDIMIENTOS EN MATERIAS TALES COMO PROPIEDAD INTELECTUAL.

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa – San Isidro
Central: 719 – 1667 / 719 – 1668 / 719 – 1669 / Telefax.: 717 – 1031
www.notariabenvenuto.com / e-mail: notario@notariabenvenuto.com

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Handwritten text, possibly a signature or date, within a rectangular box.

Handwritten text, possibly a signature or date, within a rectangular box.

TESTIMONIO

EL APODERADO ACTUANDO EN FORMA INDIVIDUAL PODRÁ DEMANDAR, RECONVENIR, CONTESTAR DEMANDAS Y RECONVENIONES, PRESENTAR TODO TIPO DE SOLICITUDES, RECURSOS, RESPUESTAS U OPOSICIONES, PRESENTAR TODO TIPO DE RECURSOS DE IMPUGNACIÓN, PRESENTAR DECLARACIONES, JURADAS O NO, PRESENTAR CUALQUIER OTRO RECURSO O REMEDIO PROCESAL PERMITIDO POR LEY, PAGAR IMPUESTOS Y ANUALIDADES, SOLICITAR TESTIMONIOS, RENUNCIAR A LOS DERECHOS DE REGISTRO SOBRE UN ELEMENTO DE LA PROPIEDAD INDUSTRIAL, DESISTIRSE DEL PROCESO Y DE LA PRETENSION, ALLANARSE A LA PRETENSION, CONCILIAR, TRANSIGIR, SOMETER A ARBITRAJE LAS PRETENSIONES CONTROVERTIDAS EN EL PROCESO, SOLICITAR Y EJECUTAR MEDIDAS CAUTELARES ASÍ COMO VISITAS INSPECTIVAS, RATIFICAR LOS ACTOS JURÍDICOS PROCESALES SUSCRITOS CON ANTERIORIDAD AL OTORGAMIENTO Y/O PRESENTACIÓN DEL PRESENTE PODER, SUSTITUIR O DELEGAR LA REPRESENTACIÓN, REVOCAR LOS PODERES OTORGADOS, RECIBIR NOTIFICACIONES EN NOMBRE DE LA COMPAÑÍA Y LOS DEMÁS ACTOS QUE EXPRESE LA LEY. =====
AGREGUE USTED SEÑOR NOTARIO, LAS CLÁUSULAS DE LEY, E INSERTE EL PODER AL QUE SE HA HECHO REFERENCIA. =====
LIMA, 21 DE JULIO DE 2010. =====

FIRMADO.- UNA FIRMA ILEGIBLE.- =====

ABOGADO QUE AUTORIZA, UN SELLO QUE DICE.- JURGEN STROBACH FLORIAN.- ABOGADO.- C.A.L. 30548.- UNA FIRMA ILEGIBLE.- =====

INSERTO UNO: TRADUCCION OFICIAL =====

MARIO GINO BENVENUTO MURGUIA, ABOGADO NOTARIO DE LIMA, CERTIFICO QUE HE TENIDO A LA VISTA LA TRADUCCION OFICIAL DEL PODER ESPECIAL, DEBIDAMENTE LEGALIZADO POR EL MINISTERIO DE RELACIONES EXTERIORES CON FECHA VEINTITRES DE JULIO DEL DOS MIL DIEZ, CUYO TENOR LITERAL ES COMO SIGUE: =====

TRADUCCIÓN OFICIAL

TRA. N° TOI.0077.10

Primera página del documento original:

PODER ESPECIAL de fecha 15 de julio de 2010 redactado en idioma castellano e inglés

Segunda página del documento original:

UR. Nr.: 1446/2010

Por la presente se certifica que las firmas que anteceden de:

- Dr. Michael Kompter, nacido el 11 de mayo de 1955, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.
- Dr. Christian Hauke, nacido el 31 de agosto de 1947, con domicilio en 55216 Ingelheim am Rhein, Binger Straße 173.

a quienes he conocido en persona, han sido estampadas en mi presencia

Asimismo, certifico que Boehringer Ingelheim International GmbH es una sociedad debidamente constituida bajo las leyes de la República Federal de

1
Estados Unidos 688 - Lima 11 Perú - Tel.: (511) 460-1659 • (511) 463-1167 • Fax: (511) 463-4548
maemm@terra.com.pe

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa - San Isidro
Central: 719 - 1667 / 719 - 1668 / 719 - 1669 / Telefax.: 717 - 1031
www.notariabenvenuto.com / e-mail: notario@notariabenvenuto.com

Página 2 de 8

TESTIMONIO

TRA. N° TOI.0077.10

Alemania, con domicilio en Binger Strasse 173, 55216
Ingelheim am Rhein, Alemania.

Dicha sociedad se encuentra inscrita en el Registro
Mercantil del Juzgado de Distrito de Bingen, bajo el
número HR B 1063 desde el 14 de mayo de 1968. Dicha
inscripción ha sido transferida por ley al Registro
Mercantil del Juzgado de Distrito de Mainz, donde se
encuentra inscrita bajo el número HR B 21063 desde el 28
de diciembre de 2005.

Asimismo, certifico que los doctores Michael Kompter y
Christian Hauke, han sido autorizados para firmar el
documento que antecede y actualmente se encuentran
debidamente autorizados para firmar a nombre de
Boehringer Ingelheim International GmbH en calidad de
apoderados.

Ingelheim am Rhein, 15 de julio de 2010

(firmado ilegible)

Notario Público

Mary Ann Montecarlo Medina
Traductora Pública Juramentada
Registro IVI N° 106

TESTIMONIO

TRA. N° TOI.0077.10

Reverso de la segunda página del documento original:

(sello en idioma extranjero distinto al inglés, de fecha 16 de julio de 2010)

(sello en idioma castellano del Consulado del Perú, de fecha 20 de julio de 2010)

(sello) MINISTERIO DE RELACIONES EXTERIORES
DIRECCIÓN GENERAL DE POLÍTICA CONSULAR

Legalización N° 092720

Se legaliza la firma que antecede del Sr.(a)
Alfredo Arecco-Sablich sin juzgar el contenido
del documento

Lima, 23 de julio de 2010

(fdo.) Maribel del Rosario LUYO JAVIER

Departamento de Legalizaciones

Dirección de Trámites Consulares/sello

La infrascrita, Traductora Pública Juramentada,
certifica que la presente traducción es fiel y
correcta del texto original en idioma Castellano.....
adjunto. Esta traducción no debe interpretarse
como reconocimiento de la autenticidad
del documento traducido.

En fe de lo cual, firmo y sello en.....Lima.....
a los...26...días del mes de...Julio...de...2010..

Mary Aníbal Montenegro Medina
Traductora Pública Juramentada
Registro JVT N° 105

MINISTERIO DE RELACIONES EXTERIORES
DIRECCIÓN GENERAL DE POLÍTICA CONSULAR
Legalización N°

Se legaliza la firma que antecede del Sr.(a)

SIN JUZGAR EL CONTENIDO DEL DOCUMENTO



Julia F. Celia Moreano de Dueñas
Departamento de Legalizaciones
Dirección de Trámites Consulares
LIMA 27 JUL 2010

Estados Unidos 888 - Lima 11 - Perú - Telfs.: (511) 460-1859 • (511) 463-1167 • Fax: (511) 463-4548
maernm@terra.com.pe

Av. Juan de Arona N° 545 Altura Cdra. 31 de la Av. Arequipa - San Isidro
Central: 719 - 1667 / 719 - 1668 / 719 - 1669 / Telefax: 717 - 1031
www.notariabenvenuto.com / e-mail: notario@notariabenvenuto.com

TESTIMONIO

FERNÁNDEZ - DÁVILA & BUENO
ABOGADOS

PODER ESPECIAL

Consta por el presente documento el Poder Especial que otorga [insertar nombre de poderdante], domiciliada en [insertar domicilio] constituida de acuerdo a las leyes de [insertar país de constitución], representada por su [insertar cargo en la cía.] Sr.(a) [insertar nombre del representante de la cía.], a favor de FERNÁNDEZ DÁVILA ABOGADOS SAC, CARLOS FERNÁNDEZ DÁVILA WINKLER, ROSA BUENO MERA, JULIETA DEL PILAR TIJERO MARTINO, DIEGO CORDOVA FLORES, IVETTE LUQUE CARDENAS y/o CLARISA SILES VASCONES, domiciliados en Av. República de Panamá 3531, Oficina 1203, San Isidro, Lima, Perú, para que la representen en la República de Perú, República de Bolivia, República de Chile, República de Colombia, República de Ecuador y República Bolivariana de Venezuela, ante cualquier autoridad administrativa o judicial, incluyendo la Secretaría y Tribunal de Justicia de la Comunidad Andina, para el inicio, tramitación, obtención, defensa y hacer respetar todas y cualquiera de las patentes de invención, modelos de utilidad, diseños industriales, marcas, lemas comerciales, nombres comerciales, protección de datos de prueba, protección de secretos empresariales, derechos de autor, registro de nombres de dominio, o seguimiento de procedimientos en materias tales como Propiedad Intelectual.

Los apoderados podrán ejercer el presente poder actuando en forma individual e indistinta, y gozarán de las siguientes facultades, tales como demandar, reconvenir, contestar demandas y reconveniciones, presentar todo tipo de solicitudes, recursos, respuestas u oposiciones, presentar todo tipo de recursos de impugnación, presentar declaraciones, juradas o no, presentar cualquier otro recurso o remedio procesal permitido por ley, pagar impuestos y anualidades, solicitar testimonios, renunciar a los derechos de registro sobre un elemento de la propiedad industrial, desistirse del proceso y de la pretensión, allanarse a la pretensión, conciliar, transigir, someter a arbitraje las pretensiones controvertidas en el proceso, solicitar y ejecutar medidas cautelares así como visitas inspectivas, ratificar los actos jurídicos procesales suscritos con anterioridad al otorgamiento y/o presentación del presente poder, sustituir o delegar la representación procesal, revocar los poderes otorgados, recibir notificaciones en nombre de la compañía y los demás actos que exprese la ley.

Suscrito en el de de 2010

ESTE PODER REQUIERE DE LEGALIZACIÓN NOTARIAL (PRECISANDO QUE EL REPRESENTANTE TIENE LAS FACULTADES PARA OTROGARLO Y QUE ESTUVO PRESENTE AL MOMENTO DE HACERLO) Y DE CONSUL PERUANO (CUANDO ES OTORGADO EN EL EXTRANJERO)

SPECIAL POWER OF ATTORNEY

By means of this Special Power of Attorney Boehringer Ingelheim International GmbH with address in Binger Strasse 173, 55216 Ingelheim am Rhein, Germany and incorporated under the laws of Germany duly represented by its Authorized Signatories Dr. Michael KOMPTER and Dr. Christian HAUKE, grants to FERNÁNDEZ DÁVILA ABOGADOS SAC, CARLOS FERNÁNDEZ DÁVILA WINKLER, ROSA BUENO MERA, JULIETA DEL PILAR TIJERO MARTINO, DIEGO CORDOVA FLORES, IVETTE LUQUE CARDENAS and/or CLARISA SILES VASCONES, with address at Av. República de Panamá 3531, Oficina 1203, San Isidro, Lima, Perú, the powers to represent in the Republic of Perú, the Republic of Bolivia, Republic of Chile, Republic of Colombia, Republic of Ecuador and the Bolivarian Republic of Venezuela before any administrative or judicial authority of any class, including the Andean Secretariat and the Andean Court of Justice to initiate, prosecution, obtain, defend and enforce any and all of the company's Patents for Invention, Utility Models, Industrial Designs, Trademarks, Trade Names, Commercial Emblems, Test Data Protection, Protection of Trade Secrets, Copyrights, Registration of Domain names and handle proceedings related to Intellectual Property.

The empowered representatives will exert this power of attorney acting individually and indistinctly with the following powers, having authority to claim, to counter-claim, to answer complaints and counter-claims, to file petitions, recourses, replies and oppositions, to withdraw the registration of an industrial property element, to abandon the action and the requested relief, to defend a suit, to file standard or sworn declarations, to file all sort of petitions, appeal and motions permitted by law, pay taxes and annuities, request testimonies, to accept in total or part the demanded pretensions, conciliate, settle, submit to arbitration the contradicted pretensions in the process, to require and execute precautionary measures and inspections among others, to ratify all the acts in regular procedures and proceedings entered into before the granting and/or presentation of this document, substitute or delegate the representation, revoke such substitutions, receive notifications on behalf of the Company and for the rest of the acts which the law provides.

Executed in Ingelheim, on 15th July of 2010

BOEHRINGER INGELHEIM INTERNATIONAL GMBH
ppa. ppa.

Dr. Michael KOMPTER
Authorized Signatory

Dr. Christian HAUKE
Authorized Signatory

THIS POWER OF ATTORNEY REQUIRES LEGALIZATION OF A NOTARY (STATING THAT THE REPRESENTATIVE HAS ENOUGH POWERS TO GRANT IT AND APPEARED AND EXECUTED IT PERSONALLY) AND OF A PERUVIAN CONSUL (WHEN GRANTED ABROAD)

Av. Juan de Arona N° 545 Allura Cdra. 31 de la Av. Arequipa - San Isidro
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www.notariabenvenuto.com / e-mail: notario@notariabenvenuto.com

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TESTIMONIO

UR. Nr. 1446/2010

It is herewith certified that above signatures of:

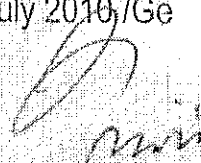
- Dr. Michael **Kompter**, born 11th day of May 1955, with its business address at 55216 Ingelheim am Rhein, Binger Straße 173,
 - Dr. Christian **Hauke**, born 31st day of August 1947, with its business address at 55216 Ingelheim am Rhein, Binger Straße 173,
- personally known,
were duly given in my presence.

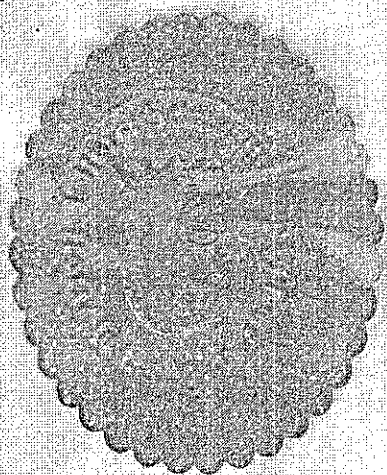
It is herewith certified that **Boehringer Ingelheim International GmbH** is a corporation duly organized and existing under the laws of the Federal Republic of Germany having its principal place of business at Binger Strasse 173, 55216 Ingelheim am Rhein, Germany.

It had been entered into the Commercial Register of the District Court of Bingen under HR B 1063 as of 14th day of May 1968. This registration was transferred by law to the Commercial Register of the District Court of Mainz, where it has been registered under HR B 21063 since 28th day of December 2005.

Furthermore, I certify that Dr. Michael Kompter and Dr. Christian Hauke were authorized to sign the foregoing document and still are duly authorized to sign on behalf as procurists of **Boehringer Ingelheim International GmbH**.

Ingelheim am Rhein, the 15th day of July 2010 /Ge


Notary public



1. *State of the world*
and the
future of the world

1910
1911

TESTIMONIO

AL DORSO: =====

910 E 1

Die Echtheit vorstehender Unterschrift des
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werden hierdurch bestätigt. Zugleich wird bescheinigt, dass der
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Kostenrechnung:

Gebühr für die Erteilung
der Legalisation:

Wert: 50.000,00 €

JVKostO v. 26.7.1957

i.V.m. § 45 KostO

Gebühr: 33,00 €

Mainz, 16.07.10

Heppes-Schwarz
Heppes-Schwarz
Amtsinspektorin



Mainz, den 16. Juli 2010
Die Präsidentin des Landgerichts
In Vertretung

Dr. Matthias Friedrich
Dr. Matthias Friedrich
Vorsitzender Richter am Landgericht

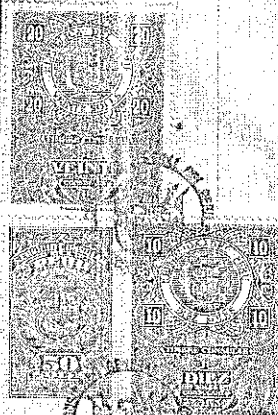
CONSULADO GENERAL DEL PERU
FRANCFORT DEL MENO

Se legaliza la firma de:
DR. MATTHIAS FRIEDRICH

Quien desempeña el cargo de:
**REPRESENTANTE DEL PRESIDENTE
DEL TRIBUNAL REGIONAL
EN MAINZ**

Nº de Orden: 0363
Nº de Asignación: AA7A
Nº de Fianza: 22.4
Derechos percibidos: S/C: 80.000 €
E: 72.000 €

Frankfurt del Meno, 20 de Julio de 2010



Alfredo Arecco-Sablich
ALFREDO ARECCO-SABLICH
Consul General del Perú



MINISTERIO DE RELACIONES EXTERIORES
DIRECCION GENERAL DE POLITICA CONSULAR

Legalización Nº 048.720

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Alfredo Arecco-Sablich
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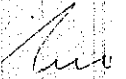
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Departamento de Legalización
Dirección de Asesoría Consular



LIMA, 23 JUL 2010

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Ramón Gortázar
Nº 1167

Mario Gino Benvenuto Murguía

ABOGADO NOTARIO DE LIMA

TESTIMONIO

INSERTO. =====

DE CONFORMIDAD CON LA LEY DEL NOTARIADO, ARTICULO 59, INCISO D), TRANSCRIBO: =====

CÓDIGO PROCESAL CIVIL: "ARTÍCULO 74.- FACULTADES GENERALES.- LA REPRESENTACIÓN JUDICIAL CONFIERE AL REPRESENTANTE LAS ATRIBUCIONES Y POTESTADES GENERALES QUE CORRESPONDEN AL REPRESENTADO, SALVO AQUELLAS PARA LAS QUE LA LEY EXIGE FACULTADES EXPRESAS. LA REPRESENTACIÓN SE ENTIENDE OTORGADA PARA TODO EL PROCESO, INCLUSO PARA LA EJECUCIÓN DE LA SENTENCIA Y EL COBRO DE COSTAS Y COSTOS, LEGITIMANDO AL REPRESENTANTE PARA SU INTERVENCIÓN EN EL PROCESO Y REALIZACIÓN DE TODOS LOS ACTOS DEL MISMO, SALVO AQUELLOS QUE REQUIERAN LA INTERVENCIÓN PERSONAL Y DIRECTA DEL REPRESENTADO." =====

CÓDIGO PROCESAL CIVIL: "ARTÍCULO 75.- FACULTADES ESPECIALES.- SE REQUIERE EL OTORGAMIENTO DE FACULTADES ESPECIALES PARA REALIZAR TODOS LOS ACTOS DE DISPOSICIÓN DE DERECHOS SUSTANTIVOS Y PARA DEMANDAR, RECONVENIR, CONTESTAR DEMANDAS Y RECONVENIONES, DESISTIRSE DEL PROCESO Y DE LA PRETENSIÓN, ALLANARSE A LA PRETENSIÓN, CONCILIAR, TRANSIGIR, SOMETER A ARBITRAJE LAS PRETENSIONES CONTROVERTIDAS EN EL PROCESO, SUSTITUIR O DELEGAR LA REPRESENTACIÓN PROCESAL Y PARA LOS DEMÁS ACTOS QUE EXPRESE LA LEY. EL OTORGAMIENTO DE FACULTADES ESPECIALES SE RIGE POR EL PRINCIPIO DE LITERALIDAD. NO SE PRESUME LA EXISTENCIA DE FACULTADES ESPECIALES NO CONFERIDAS EXPLÍCITAMENTE." =====

CONCLUSION: =====

FORMALIZADO EL INSTRUMENTO LA COMPARECIENTE LE DIO LECTURA, DESPUES DE LO CUAL SE AFIRMA Y RATIFICA EN SU CONTENIDO, DECLARANDO QUE SE TRATA DE UN ACTO VALIDO Y NO SIMULADO, MANIFESTANDO IGUALMENTE CONOCER LOS ANTECEDENTES Y/O TITULOS QUE SE ORIGINAN POR EL PRESENTE INSTRUMENTO Y DECLARANDO RECONOCER COMO SUYA LA FIRMA DE LA MINUTA QUE LA ORIGINA. =====

DEJO CONSTANCIA DE HABER ADVERTIDO A LA INTERESADA DE LOS EFECTOS LEGALES DEL PRESENTE INSTRUMENTO NOTARIAL. =====

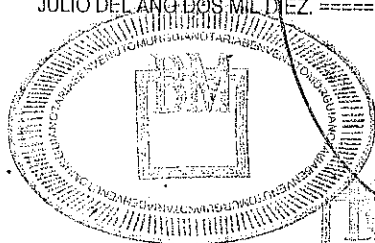
LA PRESENTE ESCRITURA PUBLICA SE INICIA EN LA FOJA DE PAPEL NOTARIAL CON NUMERO DE SERIE B Nº0706090 Y CONCLUYE EN LA FOJA DE PAPEL NOTARIAL CON NUMERO DE SERIE B Nº0706093(VUELTA), DE LO QUE DOY FE. =====

FIRMADO: JANNE IVETTE LUQUE CARDENAS.- UNA HUELLA DIGITAL.- UNA FIRMA ILEGIBLE.- FIRMÓ EL VEINTISEIS DE JULIO DEL AÑO DOS MIL DIEZ. =====

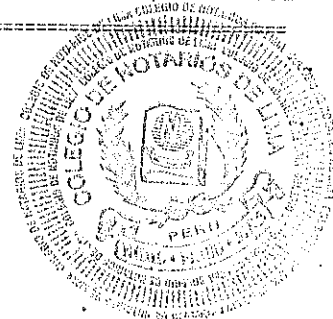
EL PROCESO DE FIRMAS CONCLUYO EL: VEINTISEIS DE JULIO DEL DOS MIL DIEZ. =====

FIRMADO: DR. MARIO GINO BENVENUTO MURGUIA. ABOGADO - NOTARIO DE LIMA. =====

ES TRANSCRIPCION DE LA ESCRITURA PUBLICA QUE CORRE EN EL REGISTRO CON FECHA VEINTISEIS DIAS DEL MES DE JULIO DEL AÑO DOS MIL DIEZ DE FOJAS 004590 A FOJAS 004593(VUELTA), Y A SOLICITUD DE PARTE INTERESADA EXPIDO EL PRESENTE, DE ACUERDO A LA LEY EL QUE RUBRICO EN CADA UNA DE SUS HOJAS, SELLO, SIGNO Y FIRMO EN LIMA, VEINTISEIS DE JULIO DEL AÑO DOS MIL DIEZ. =====



MARIO GINO BENVENUTO MURGUIA
ABOGADO
NOTARIO DE LIMA



COLEGIO DE NOTARIOS DE LIMA CERTIFICA:

la autenticidad y sellos que anteceden en esta foja
en el (la) Notario(a) de Lima,

Benvenuto Murguía

Nº 116766

Fecha:

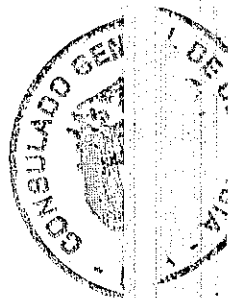
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Firma del Notario(a) más no el contenido

Av. Juan de Arona N° 546 - Urb. Cdra. 31 de la Av. Arequipa - San Isidro
Teléfono: 719 - 1667 / 719 - 1668 / 719 - 1669 / Telefax.: 717 - 1031
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Lina
Lina Gutiérrez Adriaenszén
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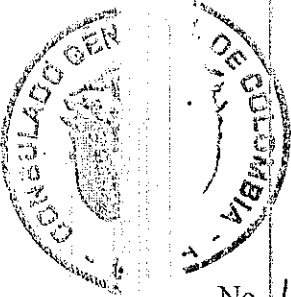
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Se legaliza la firma que antecede del Sr.(a)
Ricardo A. Laverde
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[Firma]
Julia Adela Moreano de Dueñas
Departamento de Legalizaciones
Dirección de Trámites Consulares
LIMA 27 JUL 2010





CONSULADO GENERAL DE COLOMBIA
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No. 1793

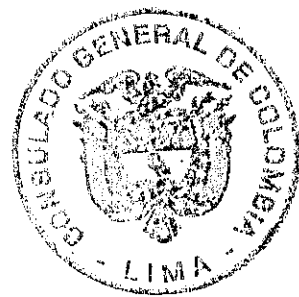
Lima, 02 Agosto 2010

El suscrito Cónsul General Consulares hace constar que el(a) señor (a) JULIA ADELA MOREANO DE DUEÑAS - DIRECION DE TRAMITES CONSULARES. Cuya firma aparece al pie del presente documento desempeñaba las funciones allí indicadas.

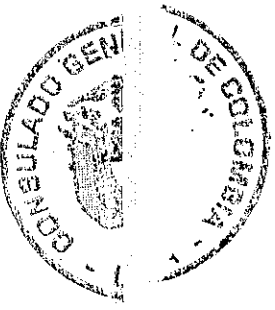
El suscrito Cónsul General no asume responsabilidad alguna por el contenido de este documento.

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Samir
JAIRO MONTES MORENO
Cónsul General



Dirección: Jorge Basadre 1580 TEL. (511) 4410530- 4410954 Fax: 2213661-4416922-4218029
Sitio Web: <http://www.embajadacolombia.org.pe/html/> - consuladogeneral@embajadacolombia.org.pe
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(71) Applicant (for all designated States except US):

BOEHRINGER INGELHEIM INTERNATIONAL GMBH [DE/DE]; Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **GREMPLER, Rolf**

[DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **JOHANSEN, Odd-Eric** [NO/NO]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173,

55216 Ingelheim Am Rhein (DE). **KLEIN, Thomas** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **LUIPPOLD, Gerd** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **MARK, Michael** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(74) Agents: **HAMMANN, Heinz** et al.; Boehringer Ingelheim GmbH, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(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, 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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, 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.

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[Continued on next page]

(54) Title: PHARMACEUTICAL COMPOSITION, METHODS FOR TREATING AND USES THEREOF

Figure 1a

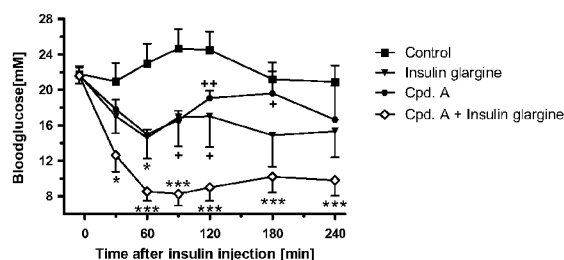
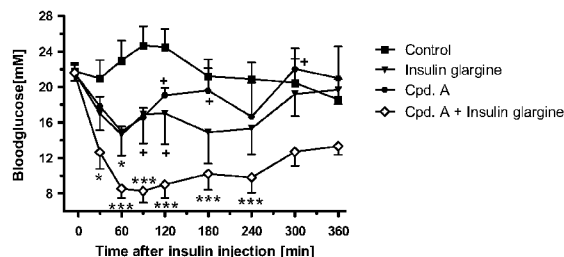


Figure 1b



(57) Abstract: The invention relates to a pharmaceutical composition according to the claim 1 comprising an SGLT2 inhibitor and an insulin which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance and hyperglycemia. In addition the present invention relates to methods for preventing or treating of metabolic disorders and related conditions.



GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, 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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

Pharmaceutical composition, methods for treating and uses thereof

Technical Field of the Invention

- 5 The invention relates to a pharmaceutical composition comprising an SGLT2-inhibitor and an insulin as described hereinafter which is suitable in the treatment or prevention of one or more conditions selected from type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose and hyperglycemia inter alia.
- 10 Furthermore the invention relates to methods
- for treating diabetes mellitus;
 - for treating diabetes mellitus, where treatment with insulin is required;
 - for treating type 1 diabetes mellitus;
 - for treating, preventing or reducing the risk of hypoglycemia;
 - 15 - for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
 - for preventing, slowing progression of, delaying, or treating a metabolic disorder;
 - for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c;
 - 20 - for preventing, slowing, delaying or reversing progression from impaired glucose tolerance, impaired fasting blood glucose, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus;
 - for reducing body weight and/or body fat or preventing or attenuating an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat;
 - 25 - for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat;
 - maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance,
 - for preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
 - 30 - for preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
 - for treating hyperuricemia and hyperuricemia associated conditions;
 - 35 - for treating or preventing kidney stones;
 - for treating hyponatremia;

- for preventing, slowing progression of, delaying, or treating diabetes related to cystic fibrosis;

in patients in need thereof characterized in that an SGLT2 inhibitor and an insulin is administered in combination or alternation.

5

In addition the present invention relates to the use of an SGLT2 inhibitor for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

In addition, the present invention relates to the use of an insulin for the manufacture of a
10 medicament for use in a method as described hereinbefore and hereinafter.

The invention also relates to a pharmaceutical composition according to this invention for use in a method as described hereinbefore and hereinafter.

- 15 The invention also relates to a use of a pharmaceutical composition according to this invention for the manufacture of a medicament for use in a method as described hereinbefore and hereinafter.

Background of the Invention

- 20 Type 1 diabetes mellitus (Type 1 diabetes), also called insulin dependent diabetes mellitus or juvenile diabetes, is a form of diabetes mellitus that results from autoimmune destruction of insulin-producing beta cells of the pancreas. The subsequent lack of insulin leads to increased blood glucose concentrations and increased urinary glucose excretion. The classical symptoms are polyuria, polydipsia, polyphagia, and weight loss. Type 1 diabetes
25 may be fatal unless treated with insulin. Complications may be associated with both hypoglycemic and hyperglycemic states. Serious hypoglycemia may lead to seizures or episodes of unconsciousness requiring emergency treatment. Uncontrolled hyperglycemia and insufficient insulin may lead to severe ketoacidosis which could be fatal. Hyperglycaemia per se might also in the short term lead to tiredness and visual disturbances and can also
30 result in long term damage to organs such as eyes, kidneys and joints. Subcutaneous injections are the most common method of administering insulin although inhaled insulin, as well as oral formulations, are being tested in clinical trials. Rapid acting insulin analogs have been developed which are more readily absorbed from the injection site and therefore act faster than rapid human insulin injected subcutaneously, intended to supply the bolus level of
35 insulin needed after a meal. Other insulin analogs - so called long acting insulins (for example glargine insulin, detemir insulin) - are available which are released slowly over a

period of time, for example 8 to 24 hours, intended to supply the basal level of insulin for the day.

Type 2 diabetes is an increasingly prevalent disease that due to a high frequency of

5 complications associated with a reduction in life expectancy. Because of diabetes-associated microvascular complications, type 2 diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputations in the industrialized world. In addition, the presence of type 2 diabetes is associated with a two to five fold increase in cardiovascular disease risk.

10

After long duration of disease, most patients with type 2 diabetes will eventually fail on oral therapy and become insulin dependent with the necessity for daily injections and multiple daily glucose measurements.

15 The UKPDS (United Kingdom Prospective Diabetes Study) demonstrated that intensive treatment with metformin, sulfonylureas or insulin resulted in only a limited improvement of glycemic control (difference in HbA1c ~0.9%) as compared to conventional treatment. In addition, even in patients within the intensive treatment arm glycemic control deteriorated significantly over time and this was attributed to deterioration of beta-cell function. Of
20 importance however, despite this deterioration of beta-cell function, was that intensive glycaemic treatment was associated with microvascular benefits in the short term (6 years) and macro-mascular benefits in the long term (15 years). Similar phenomenon has also been demonstrated in patients with type 1 diabetes mellitus, e.g. in the diabetes control and complications trial (DCCT) where a difference in the median HbA1c (~1.9%) between the
25 conventional therapy and intensive therapy group during 6.5 years of study, led to significant relative risk reductions for microvascular complications whereas macrovascular benefits was noted 11 years after the DCCT, e.g. as reported in the EDIC (Epidemiology of Diabetes Interventions and Complications) study, where a relative HbA1c reduction by 10% in one
30 patient compared to another was associated with a hazard ratio of 0.80 for cardiovascular complications. Despite such convincing long term effects of glycaemic management many patients with type 2 diabetes or type 1 diabetes remain inadequately treated, partly because of limitations in long term efficacy, tolerability and dosing inconvenience of existing antihyperglycemic therapies.

Oral antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or (initial or add-on) combination therapy) include, without being restricted thereto, metformin, sulphonylureas, thiazolidinediones, glinides and α -glucosidase inhibitors.

- 5 The high incidence of therapeutic failure might be a major contributor to the high rate of long-term hyperglycemia-associated complications or chronic damages (including micro- and macrovascular complications such as e.g. diabetic nephropathy, retinopathy or neuropathy, or cardiovascular complications) in patients with type 2 diabetes or type 1 diabetes.
- 10 Therefore, there is an unmet medical need for methods, medicaments and pharmaceutical compositions with a good efficacy with regard to glycemic control, with regard to disease-modifying properties and with regard to reduction of cardiovascular morbidity and mortality while at the same time showing an improved safety profile.
- 15 SGLT2 inhibitors represent a novel class of agents that are being developed for the treatment or improvement in glycemic control in patients with type 2 diabetes. Glucopyranosyl-substituted benzene derivative are described in the prior art as SGLT2 inhibitors, for example in WO 01/27128, WO 03/099836, WO 2005/092877, WO 2006/034489, WO 2006/064033, WO 2006/117359, WO 2006/117360, WO 2007/025943, 20 WO 2007/028814, WO 2007/031548, WO 2007/093610, WO 2007/128749, WO 2008/049923, WO 2008/055870, WO 2008/055940. The glucopyranosyl-substituted benzene derivatives are proposed as inducers of urinary sugar excretion and as medicaments in the treatment of diabetes.
- 25 Renal filtration and reuptake of glucose contributes, among other mechanisms, to the steady state plasma glucose concentration and can therefore serve as an antidiabetic target. Reuptake of filtered glucose across epithelial cells of the kidney proceeds via sodium-dependent glucose cotransporters (SGLTs) located in the brush-border membranes in the tubuli along the sodium gradient. There are at least 3 SGLT isoforms that differ in their 30 expression pattern as well as in their physico-chemical properties. SGLT2 is exclusively expressed in the kidney, whereas SGLT1 is expressed additionally in other tissues like intestine, colon, skeletal and cardiac muscle. SGLT3 has been found to be a glucose sensor in interstitial cells of the intestine without any transport function. Potentially, other related, but not yet characterized genes, may contribute further to renal glucose reuptake. Under 35 normoglycemia, glucose is completely reabsorbed by SGLTs in the kidney, whereas the reuptake capacity of the kidney is saturated at glucose concentrations higher than 10mM,

resulting in glucosuria (hence the notion "diabetes mellitus"). This threshold concentration can be decreased by SGLT2-inhibition. It has been shown in experiments with the SGLT inhibitor phlorizin that SGLT-inhibition will partially inhibit the reuptake of glucose from the glomerular filtrate into the blood leading to a decrease in blood glucose concentrations and to glucosuria.

Aim of the present invention

The aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular of diabetes mellitus and complications of diabetes mellitus.

Another aim of the present invention is to provide a pharmaceutical composition and method for treating patients with type 1 diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient in need thereof, in particular in patients with type 1 or type 2 diabetes mellitus.

Another aim of the present invention is to provide a pharmaceutical composition and method for improving glycemic control in a patient.

Another aim of the present invention is to provide a pharmaceutical composition and method for prolonging the duration of efficacy of an insulin administered to a patient.

Another aim of the present invention is to provide a pharmaceutical composition and method for reducing the required insulin dose in a patient.

Another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing or delaying progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic syndrome to type 2 diabetes mellitus.

Yet another aim of the present invention is to provide a pharmaceutical composition and method for preventing, slowing progression of, delaying or treating of a condition or disorder from the group consisting of complications of diabetes mellitus, in particular type 1 or type 2 diabetes mellitus.

A further aim of the present invention is to provide a pharmaceutical composition and method for reducing the weight or preventing or attenuating an increase of the weight in a patient in need thereof.

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Another aim of the present invention is to provide a new pharmaceutical composition with a high efficacy for the treatment of metabolic disorders, in particular of diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), and/or hyperglycemia, which has good to very good pharmacological and/or pharmacokinetic and/or physicochemical properties.

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Further aims of the present invention become apparent to the one skilled in the art by description hereinbefore and in the following and by the examples.

15 **Summary of the Invention**

Within the scope of the present invention it has now surprisingly been found that a combination of a SGLT2 inhibitor and an insulin leads to a higher blood glucose lowering compared with a treatment using the insulin or the SGLT2 inhibitor alone. Thus in order to achieve a certain level of baseline blood glucose the dose of the insulin may be reduced by using a combination of a SGLT2 inhibitor and an insulin. Furthermore it has surprisingly been found that an administration of a SGLT2 inhibitor in a time period after the administration of an insulin prolongs the lowering of the blood glucose compared with an administration of the insulin alone.

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Therefore a combination of a SGLT2 inhibitor and an insulin can advantageously be used for preventing, slowing progression of, delaying or treating a metabolic disorder, in particular for improving glycemic control in patients. This opens up new therapeutic possibilities in the treatment and prevention of type 1 diabetes mellitus, type 2 diabetes mellitus, complications of diabetes mellitus and of neighboring disease states.

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Therefore, in a first aspect the present invention provides a pharmaceutical composition comprising

(a) an SGLT2 inhibitor, and

(b) an insulin.

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According to another aspect of the invention, there is provided a method for treating diabetes mellitus in a patient characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

5 According to another aspect of the invention, there is provided a method for treating diabetes mellitus in a patient where treatment with insulin is required characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

10 According to another aspect of the invention, there is provided a method for treating type 1 diabetes mellitus in a patient characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

According to another aspect of the invention, there is provided a method for treating,
15 preventing or reducing the risk of hypoglycemia in a patient characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

According to another aspect of the invention, there is provided a method for preventing,
20 slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease,
25 cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis, in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient. In particular one or more aspects of diabetic nephropathy such as hyperperfusion, proteinuria and albuminuria may be treated, their progression slowed or their onset delayed or prevented. The term "tissue ischaemia"
30 particularly comprises diabetic macroangiopathy, diabetic microangiopathy, impaired wound healing and diabetic ulcer. The terms "micro- and macrovascular diseases" and "micro- and macrovascular complications" are used interchangeably in this application.

According to another aspect of the invention, there is provided a method for preventing,
35 slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting

blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, gestational diabetes and diabetes related to cystic fibrosis in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

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According to another aspect of the invention, there is provided a method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or

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alternation, to the patient.

The pharmaceutical composition according to this invention may also have valuable disease-modifying properties with respect to diseases or conditions related to impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or metabolic

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syndrome.

According to another aspect of the invention, there is provided a method for preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2

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diabetes mellitus in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

As by the use of a pharmaceutical composition according to this invention, an improvement of the glycemic control in patients in need thereof is obtainable, also those conditions and/or

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diseases related to or caused by an increased blood glucose level may be treated.

By the administration of a pharmaceutical composition according to this invention and due to the activity of the SGLT2 inhibitor excessive blood glucose levels are not converted to insoluble storage forms, like fat, but excreted through the urine of the patient. In animal

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models using a SGLT2 inhibitor it can be seen that loss of fat accounts for the majority of the observed weight loss whereas no significant changes in body water or protein content are observed. Therefore, no or less gain in weight or even a reduction in body weight is the result.

According to another aspect of the invention, there is provided a method for reducing body weight and/or body fat or preventing or attenuating an increase in body weight and/or body

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fat or facilitating a reduction in body weight and/or body fat in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

- 5 By the administration of a combination or pharmaceutical composition according to the present invention, an abnormal accumulation of ectopic fat, in particular of the liver, may be reduced or inhibited. Therefore, according to another aspect of the present invention, there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat, in particular of the liver, in a patient in
10 need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient. Diseases or conditions which are attributed to an abnormal accumulation of liver fat are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver
15 or toxic fatty liver.

- As a result thereof, another aspect of the invention provides a method for maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance in a patient in need thereof characterized in that an SGLT2 inhibitor and an
20 insulin are administered, for example in combination or alternation, to the patient.

- According to another aspect of the invention, there is provided a method for preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS) in a patient in need thereof
25 characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

- According to a further aspect of the invention, there is provided a method for preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and
30 macrovascular diseases and events, graft rejection, infection, and death in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

- According to another aspect of the invention, there is provided a method for preventing,
35 slowing progression of, delaying, or treating diabetes associated with cystic fibrosis in a

patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

The pharmaceutical composition according to the invention is capable of facilitating the lowering of serum total urate levels in the patient. Therefore according to another aspect of the invention, there is provided a method for treating hyperuricemia and hyperuricemia-associated conditions, such as for example gout, hypertension and renal failure, in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

The administration of a pharmaceutical composition increases the urine excretion of glucose. This increase in osmotic excretion and water release and the lowering of urate levels are beneficial as a treatment or prevention for kidney stones. Therefore in a further aspect of the invention, there is provided a method for treating or preventing kidney stones in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient.

According to a further aspect of the invention, there is provided a method for treating hyponatremia, water retention and water intoxication in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient. By the administration of the pharmaceutical composition according to this invention it may be possible to reverse the effects of hyponatremia, water retention and water intoxication by acting on the kidney to reverse water retention and electrolyte imbalances associated with these diseases and disorders.

According to another aspect of the invention there is provided the use of an SGLT2 inhibitor for the manufacture of a medicament for

- treating diabetes mellitus;
- treating diabetes mellitus, where treatment with insulin is required;
- treating type 1 diabetes mellitus;
- treating, preventing or reducing the risk of hypoglycemia;
- preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
- preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia,

postprandial hyperglycemia, overweight, obesity, metabolic syndrome and gestational diabetes; or

- improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
- 5 - preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, 10 tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or
- reducing body weight and/or body fat or preventing or attenuating an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat; or
- 15 - preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat; or
- maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
- preventing, slowing progression of, delaying, or treating new onset diabetes after 20 transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
- preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
- treating diabetes associated with cystic fibrosis
- 25 - treating hyperuricemia and hyperuricemia associated conditions;
- treating or prevention kidney stones;
- treating hyponatremia;

in a patient in need thereof characterized in that the SGLT2 inhibitor is administered, for example in combination or alternation, with an insulin.

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According to another aspect of the invention, there is provided the use of an insulin for the manufacture of a medicament for

- treating diabetes mellitus;
- treating diabetes mellitus, where treatment with insulin is required;
- 35 - treating type 1 diabetes mellitus;
- treating, preventing or reducing the risk of hypoglycemia;

- preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
 - preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), hyperglycemia, postprandial hyperglycemia, overweight, obesity and metabolic syndrome; or
 - improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
 - preventing, slowing, delaying or reversing progression from impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
 - preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, arteriosclerosis, myocardial infarction, stroke and peripheral arterial occlusive disease; or
 - reducing body weight and/or body fat or preventing or attenuating an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat; or
 - preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat; or
 - maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
- in a patient in need thereof characterized in that the insulin is administered, for example in combination or alternation, with an SGLT2 inhibitor.

According to another aspect of the invention, there is provided the use of a pharmaceutical composition according to the present invention for the manufacture of a medicament for a therapeutic and preventive method as described hereinbefore and hereinafter.

Definitions

The term "**active ingredient**" of a pharmaceutical composition according to the present invention means the SGLT2 inhibitor and/or the long acting insulin according to the present invention.

The term "**body mass index**" or "**BMI**" of a human patient is defined as the weight in kilograms divided by the square of the height in meters, such that BMI has units

of kg/m².

The term "**overweight**" is defined as the condition wherein the individual has a BMI greater than or 25 kg/m² and less than 30 kg/m². The terms "overweight" and "pre-obese" are used
5 interchangeably.

The term "**obesity**" is defined as the condition wherein the individual has a BMI equal to or greater than 30 kg/m². According to a WHO definition the term obesity may be categorized as follows: the term "class I obesity" is the condition wherein the BMI is equal to or greater
10 than 30 kg/m² but lower than 35 kg/m²; the term "class II obesity" is the condition wherein the BMI is equal to or greater than 35 kg/m² but lower than 40 kg/m²; the term "class III obesity" is the condition wherein the BMI is equal to or greater than 40 kg/m².

The term "**visceral obesity**" is defined as the condition wherein a waist-to-hip ratio of
15 greater than or equal to 1.0 in men and 0.8 in women is measured. It defines the risk for insulin resistance and the development of pre-diabetes.

The term "**abdominal obesity**" is usually defined as the condition wherein the waist circumference is > 40 inches or 102 cm in men, and is > 35 inches or 94 cm in women. With
20 regard to a Japanese ethnicity or Japanese patients abdominal obesity may be defined as waist circumference ≥ 85 cm in men and ≥ 90 cm in women (see e.g. investigating committee for the diagnosis of metabolic syndrome in Japan).

The term "**euglycemia**" is defined as the condition in which a subject has a fasting blood
25 glucose concentration within the normal range, greater than 70 mg/dL (3.89 mmol/L) and less than 100 mg/dL (5.6 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term "**hyperglycemia**" is defined as the condition in which a subject has a fasting blood
30 glucose concentration above the normal range, greater than 100 mg/dL (5.6 mmol/L). The word "fasting" has the usual meaning as a medical term.

The term "**hypoglycemia**" is defined as the condition in which a subject has a blood glucose concentration below the normal range, in particular below 70 mg/dL (3.89 mmol/L) or even
35 below 60 mg/dl.

The term "**postprandial hyperglycemia**" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 200 mg/dL (11.1 mmol/L).

- 5 The term "**impaired fasting blood glucose**" or "**IFG**" is defined as the condition in which a subject has a fasting blood glucose concentration or fasting serum glucose concentration in a range from 100 to 125 mg/dl (i.e. from 5.6 to 6.9 mmol/l), in particular greater than 110 mg/dL and less than 126 mg/dl (7.00 mmol/L). A subject with "normal fasting glucose" has a fasting glucose concentration smaller than 100 mg/dl, i.e. smaller than 5.6 mmol/l.

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The term "**impaired glucose tolerance**" or "**IGT**" is defined as the condition in which a subject has a 2 hour postprandial blood glucose or serum glucose concentration greater than 140 mg/dl (7.8 mmol/L) and less than 200 mg/dL (11.11 mmol/L). The abnormal glucose tolerance, i.e. the 2 hour postprandial blood glucose or serum glucose concentration can be
15 measured as the blood sugar level in mg of glucose per dL of plasma 2 hours after taking 75 g of glucose after a fast. A subject with "normal glucose tolerance" has a 2 hour postprandial blood glucose or serum glucose concentration smaller than 140 mg/dl (7.8 mmol/L).

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The term "**hyperinsulinemia**" is defined as the condition in which a subject with insulin resistance, with or without euglycemia, has fasting or postprandial serum or plasma insulin concentration elevated above that of normal, lean individuals without insulin resistance, having a waist-to-hip ratio < 1.0 (for men) or < 0.8 (for women).

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The terms "insulin-sensitizing", "insulin resistance-improving" or "insulin resistance-lowering" are synonymous and used interchangeably.

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The term "**insulin resistance**" is defined as a state in which circulating insulin levels in excess of the normal response to a glucose load are required to maintain the euglycemic state (Ford ES, *etal. JAMA. (2002) 287:356-9*). A method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so called minimal models in which, during an intravenous glucose tolerance test, the insulin and
35 glucose concentrations in the blood are measured at fixed time intervals and from these the

insulin resistance is calculated. With this method, it is not possible to distinguish between hepatic and peripheral insulin resistance.

Furthermore, insulin resistance, the response of a patient with insulin resistance to therapy, insulin sensitivity and hyperinsulinemia may be quantified by assessing the “homeostasis model assessment to insulin resistance (HOMA-IR)” score, a reliable indicator of insulin resistance (Katsuki A, *et al.* Diabetes Care 2001; 24: 362-5). Further reference is made to methods for the determination of the HOMA-index for insulin sensitivity (*Matthews et al., Diabetologia* 1985, 28: 412-19), of the ratio of intact proinsulin to insulin (*Forst et al., Diabetes* 2003, 52(Suppl.1): A459) and to an euglycemic clamp study. In addition, plasma adiponectin levels can be monitored as a potential surrogate of insulin sensitivity. The estimate of insulin resistance by the homeostasis assessment model (HOMA)-IR score is calculated with the formula (Galvin P, *et al.* Diabet Med 1992;9:921-8):

$$\text{HOMA-IR} = [\text{fasting serum insulin } (\mu\text{U/mL})] \times [\text{fasting plasma glucose}(\text{mmol/L})/22.5]$$

As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

Patients with a predisposition for the development of IGT or IFG or type 2 diabetes are those having euglycemia with hyperinsulinemia and are by definition, insulin resistant. A typical patient with insulin resistance is usually overweight or obese, but this is not always the case. If insulin resistance can be detected, this is a particularly strong indication of the presence of pre-diabetes. Thus, it may be that in order to maintain glucose homeostasis a person have e.g. 2-3 times as high endogenous insulin production as a healthy person, without this resulting in any clinical symptoms.

The methods to investigate the **function of pancreatic beta-cells** are similar to the above methods with regard to insulin sensitivity, hyperinsulinemia or insulin resistance: An improvement of beta-cell function can be measured for example by determining a HOMA-index for beta-cell function (*Matthews et al., Diabetologia* 1985, 28: 412-19), the ratio of intact proinsulin to insulin (*Forst et al., Diabetes* 2003, 52(Suppl.1): A459), the insulin/C-peptide secretion after an oral glucose tolerance test or a meal tolerance test, or by employing a hyperglycemic clamp study and/or minimal modeling after a frequently sampled intravenous glucose tolerance test (*Stumvoll et al., Eur J Clin Invest* 2001, 31: 380-81).

The term “**pre-diabetes**” is the condition wherein an individual is pre-disposed to the development of type 2 diabetes. Pre-diabetes extends the definition of impaired glucose tolerance to include individuals with a fasting blood glucose within the high normal range $\geq$ 100 mg/dL (J. B. Meigs, *et al.* Diabetes 2003; 52:1475-1484) and fasting hyperinsulinemia (elevated plasma insulin concentration). The scientific and medical basis for identifying pre-diabetes as a serious health threat is laid out in a Position Statement entitled "The Prevention or Delay of Type 2 Diabetes" issued jointly by the American Diabetes Association and the National Institute of Diabetes and Digestive and Kidney Diseases (Diabetes Care 2002; 25:742-749).

Individuals likely to have insulin resistance are those who have two or more of the following attributes: 1) overweight or obese, 2) high blood pressure, 3) hyperlipidemia, 4) one or more 1st degree relative with a diagnosis of IGT or IFG or type 2 diabetes. Insulin resistance can be confirmed in these individuals by calculating the HOMA-IR score. For the purpose of this invention, insulin resistance is defined as the clinical condition in which an individual has a HOMA-IR score > 4.0 or a HOMA-IR score above the upper limit of normal as defined for the laboratory performing the glucose and insulin assays.

The term “**type 1 diabetes**” is defined as the condition in which a subject has, in the presence of autoimmunity towards the pancreatic beta-cell or insulin, a fasting blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dL (11.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach, in the presence of autoimmunity towards the pancreatic beta cell or insulin. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. The presence of autoimmunity towards the pancreatic beta-cell may be observed by detection of circulating islet cell autoantibodies [“type 1A diabetes mellitus”], i.e., at least one of: GAD65 [glutamic acid decarboxylase-65], ICA [islet-cell cytoplasm], IA-2 [intracytoplasmatic domain of the tyrosine phosphatase-like protein IA-2], ZnT8 [zinc-transporter-8] or anti-insulin; or other signs of autoimmunity without the presence of typical circulating autoantibodies [type 1B diabetes], i.e. as detected through pancreatic biopsy or imaging). Typically a genetic predisposition is present (e.g. HLA, *INS* VNTR and *PTPN22*), but this is not always the case.

The term **"type 2 diabetes"** is defined as the condition in which a subject has a fasting blood glucose or serum glucose concentration greater than 125 mg/dL (6.94 mmol/L). The measurement of blood glucose values is a standard procedure in routine medical analysis. If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 200 mg of glucose per dL (11.1 mmol/l) of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject, the blood sugar level before taking the glucose will be between 60 and 110 mg per dL of plasma, less than 200 mg per dL 1 hour after taking the glucose and less than 140 mg per dL after 2 hours. If after 2 hours the value is between 140 and 200 mg, this is regarded as abnormal glucose tolerance.

The term **"late stage type 2 diabetes mellitus"** includes patients with a secondary drug failure, indication for insulin therapy and progression to micro- and macrovascular complications e.g. diabetic nephropathy, or coronary heart disease (CHD).

The term **"HbA1c"** refers to the product of a non-enzymatic glycation of the haemoglobin B chain. Its determination is well known to one skilled in the art. In monitoring the treatment of diabetes mellitus the HbA1c value is of exceptional importance. As its production depends essentially on the blood sugar level and the life of the erythrocytes, the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar levels of the preceding 4-6 weeks. Diabetic patients whose HbA1c value is consistently well adjusted by intensive diabetes treatment (i.e. < 6.5 % of the total haemoglobin in the sample), are significantly better protected against diabetic microangiopathy. For example, metformin on its own achieves an average improvement in the HbA1c value in the diabetic of the order of 1.0 – 1.5 %. This reduction of the HbA1C value is not sufficient in all diabetics to achieve the desired target range of < 6.5 % and preferably < 6 % HbA1c.

The term **"insufficient glycemic control"** or "inadequate glycemic control" in the scope of the present invention means a condition wherein patients show HbA1c values above 6.5 %, in particular above 7.0 %, even more preferably above 7.5 %, especially above 8 %.

The **"metabolic syndrome"**, also called "syndrome X" (when used in the context of a metabolic disorder), also called the "dysmetabolic syndrome" is a syndrome complex with the cardinal feature being insulin resistance (Laaksonen DE, *et al. Am J Epidemiol*

2002;**156**:1070-7). According to the ATP III/NCEP guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) *JAMA: Journal of the American Medical Association* (2001) **285**:2486-2497),

5 diagnosis of the metabolic syndrome is made when three or more of the following risk factors are present:

1. Abdominal obesity, defined as waist circumference > 40 inches or 102 cm in men, and > 35 inches or 94 cm in women; or with regard to a Japanese ethnicity or Japanese patients defined as waist circumference $\geq$ 85 cm in men and $\geq$ 90 cm in women;
- 10 2. Triglycerides: $\geq$ 150 mg/dL
3. HDL-cholesterol < 40 mg/dL in men
4. Blood pressure $\geq$ 130/85 mm Hg (SBP $\geq$ 130 or DBP $\geq$ 85)
5. Fasting blood glucose $\geq$ 100 mg/dL

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The NCEP definitions have been validated (Laaksonen DE, *et al. Am J Epidemiol.* (2002) **156**:1070-7). Triglycerides and HDL cholesterol in the blood can also be determined by standard methods in medical analysis and are described for example in Thomas L (Editor): "Labor und Diagnose", TH-Books Verlagsgesellschaft mbH, Frankfurt/Main, 2000.

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According to a commonly used definition, **hypertension** is diagnosed if the systolic blood pressure (SBP) exceeds a value of 140 mm Hg and diastolic blood pressure (DBP) exceeds a value of 90 mm Hg. If a patient is suffering from manifest diabetes it is currently recommended that the systolic blood pressure be reduced to a level below 130 mm Hg and the diastolic blood pressure be lowered to below 80 mm Hg.

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The definitions of **NODAT** (new onset diabetes after transplantation) and **PTMS** (post-transplant metabolic syndrome) follow closely that of the American Diabetes Association diagnostic criteria for type 2 diabetes, and that of the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute, for the metabolic syndrome. NODAT and/or PTMS are associated with an increased risk of micro- and macrovascular disease and events, graft rejection, infection, and death. A number of predictors have been identified as potential risk factors related to NODAT and/or PTMS including a higher age at transplant, male gender, the pre-transplant body mass index, pre-transplant diabetes, and immunosuppression.

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The term "**gestational diabetes**" (diabetes of pregnancy) denotes a form of the diabetes which develops during pregnancy and usually ceases again immediately after the birth. Gestational diabetes is diagnosed by a screening test which is carried out between the 24th and 28th weeks of pregnancy. It is usually a simple test in which the blood sugar level is measured one hour after the administration of 50 g of glucose solution. If this 1 h level is above 140 mg/dl, gestational diabetes is suspected. Final confirmation may be obtained by a standard glucose tolerance test, for example with 75 g of glucose.

The term "**hyperuricemia**" denotes a condition of high serum total urate levels. In human blood, uric acid concentrations between 3.6 mg/dL (ca. 214 μ mol/L) and 8.3 mg/dL (ca. 494 μ mol/L) are considered normal by the American Medical Association. High serum total urate levels, or hyperuricemia, are often associated with several maladies. For example, high serum total urate levels can lead to a type of arthritis in the joints known as gout. Gout is a condition created by a build up of monosodium urate or uric acid crystals on the articular cartilage of joints, tendons and surrounding tissues due to elevated concentrations of total urate levels in the blood stream. The build up of urate or uric acid on these tissues provokes an inflammatory reaction of these tissues. Saturation levels of uric acid in urine may result in kidney stone formation when the uric acid or urate crystallizes in the kidney. Additionally, high serum total urate levels are often associated with the so-called metabolic syndrome, including cardiovascular disease and hypertension.

The term "**hyponatremia**" denotes a condition of a positive balance of water with or without a deficit of sodium, which is recognized when the plasma sodium falls below the level of 135 mmol/L. Hyponatremia is a condition which can occur in isolation in individuals that over-consume water; however, more often hyponatremia is a complication of medication or other underlying medical condition that leads to a diminished excretion of water. Hyponatremia may lead to water intoxication, which occurs when the normal tonicity of extracellular fluid falls below the safe limit, due to retention of excess water. Water intoxication is a potentially fatal disturbance in brain function. Typical symptoms of water intoxication include nausea, vomiting, headache and malaise.

The term "**SGLT2 inhibitor**" in the scope of the present invention relates to a compound, in particular to a glucopyranosyl-derivative, i.e. compound having a glucopyranosyl-moiety, which shows an inhibitory effect on the sodium-glucose transporter 2 (SGLT2), in particular the human SGLT2. The inhibitory effect on hSGLT2 measured as IC₅₀ is preferably below 1000 nM, even more preferably below 100 nM, most preferably below 50 nM. IC₅₀ values of

SGLT2 inhibitors are usually above 0.01 nM, or even equal to or above 0.1 nM. The inhibitory effect on hSGLT2 can be determined by methods known in the literature, in particular as described in the application WO 2005/092877 or WO 2007/093610 (pages 23/24), which are incorporated herein by reference in its entirety. The term "SGLT2 inhibitor" also comprises any pharmaceutically acceptable salts thereof, hydrates and solvates thereof, including the respective crystalline forms.

The term "**insulin**" in the scope of the present invention relates to insulin and insulin analogs being used in the therapy of patients, in particular humans, which includes normal insulin, human insulin, insulin derivatives, zinc insulins and insulin analogues, including formulations thereof with modified release profiles. in particular as used in the therapy of humans. The term "insulin" in the scope of the present invention covers the following types of insulins:

- rapid-acting insulins,

- short-acting insulins,

- intermediate-acting insulins,

- long-acting insulins,

and mixtures thereof, for example mixtures of short- or rapid-acting insulins with long-acting insulins. The term "insulin" in the scope of the present invention covers insulins which are administered to the patient via injection, via infusion, including pumps, via inhalation, via oral, via transdermal or other routes of administration.

The terms "**treatment**" and "treating" comprise therapeutic treatment of patients having already developed said condition, in particular in manifest form. Therapeutic treatment may be symptomatic treatment in order to relieve the symptoms of the specific indication or causal treatment in order to reverse or partially reverse the conditions of the indication or to stop or slow down progression of the disease. Thus the compositions and methods of the present invention may be used for instance as therapeutic treatment over a period of time as well as for chronic therapy.

The terms "**prophylactically treating**", "preventively treating" and "preventing" are used interchangeably and comprise a treatment of patients at risk to develop a condition mentioned hereinbefore, thus reducing said risk.

Brief Description of the Figures

The Figure 1 shows the blood glucose line in rats after administration of a SGLT2 inhibitor, insulin glargine and a combination thereof.

The Figure 2 shows the blood glucose line in rats after administration of a low-dose insulin glargine, a high dose insulin glargine and a combination of a SGLT2 inhibitor with a low dose of insulin glargine.

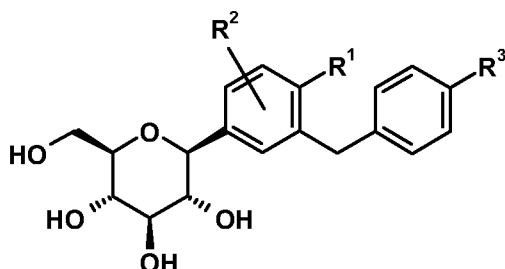
The Figure 3 shows the blood glucose line in rats after administration of insulin glargine and a co-administration of a SGLT2 inhibitor after 120 minutes.

The Figure 4 shows the effect on body fat portion after implantation of insulin-releasing sticks and after administration of a SGLT2 inhibitor alone and in addition to the implants.

Detailed Description

The aspects according to the present invention, in particular the pharmaceutical compositions, methods and uses, refer to SGLT2 inhibitors and insulins. In the methods and uses according to this invention a third antidiabetic agent may optionally be administered, i.e. the SGLT2 inhibitor and the insulin are administered in combination without a third antidiabetic agent or with a third antidiabetic agent.

Preferably the SGLT2 inhibitor is selected from the **group G1** consisting of dapagliflozin, canagliflozin, atigliflozin, ipragliflozin, tofogliflozin, remogliflozin, sergliflozin and glucopyranosyl-substituted benzene derivatives of the formula (I)



wherein R^1 denotes Cl, methyl or cyano; R^2 denotes H, methyl, methoxy or hydroxy and R^3 denotes ethyl, cyclopropyl, ethynyl, ethoxy, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy; or a prodrug of one of the beforementioned SGLT2 inhibitors.

Compounds of the formula (I) and methods of their synthesis are described for example in the following patent applications: WO 2005/092877, WO 2006/117360, WO 2006/117359, WO 2006/120208, WO 2006/064033, WO 2007/031548, WO 2007/093610, WO 2008/020011, WO 2008/055870.

In the above glucopyranosyl-substituted benzene derivatives of the formula (I) the following definitions of the substituents are preferred.

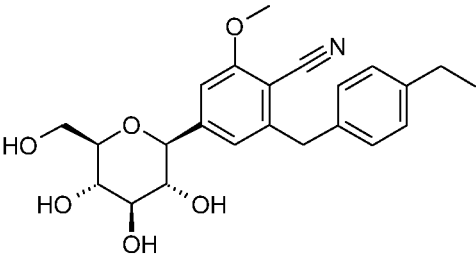
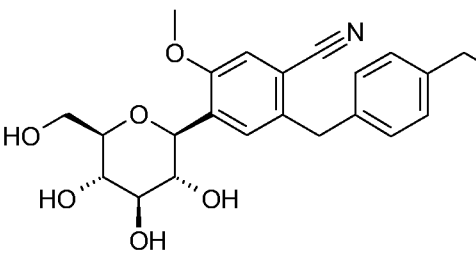
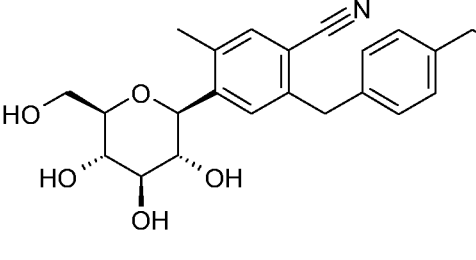
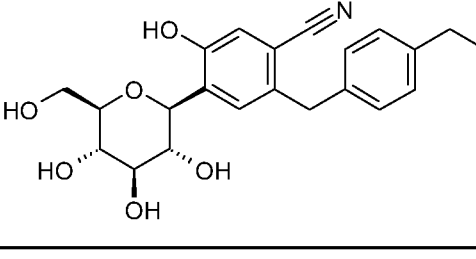
Preferably R^1 denotes chloro or cyano; in particular chloro.

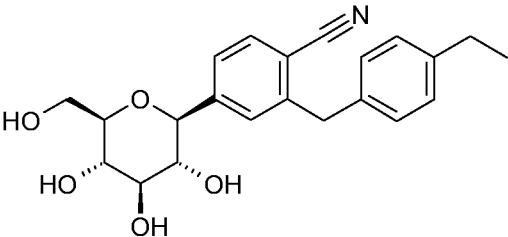
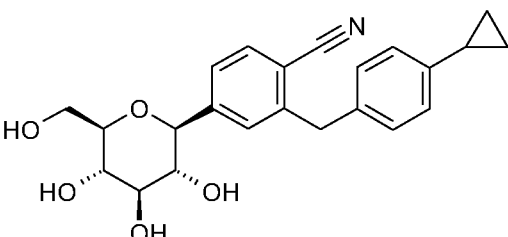
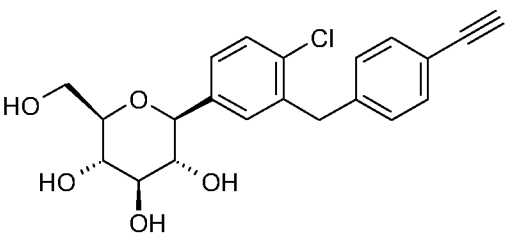
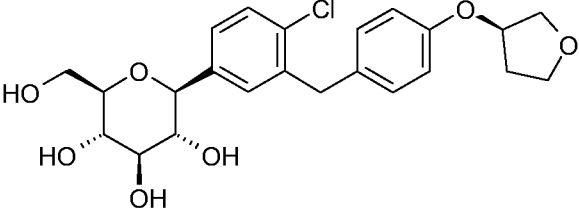
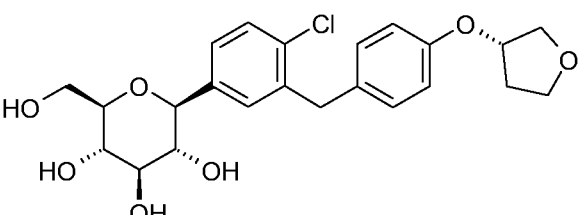
Preferably R^2 denotes H.

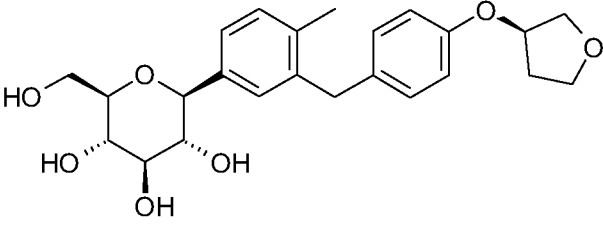
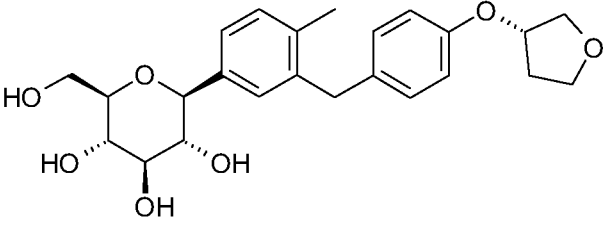
Preferably R^3 denotes ethyl, cyclopropyl, ethynyl, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy. Even more preferably R^3 denotes cyclopropyl, ethynyl, (*R*)-

- 5 tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy. Most preferably R^3 denotes ethynyl, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy.

Preferred glucopyranosyl-substituted benzene derivatives of the formula (I) are selected from the group of compounds (I.1) to (I.11):

(I.1)	 6-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-2-methoxy-benzonitrile,
(I.2)	 2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methoxy-benzonitrile,
(I.3)	 1-cyano-2-(4-ethylbenzyl)-4-(β-D-glucopyranos-1-yl)-5-methyl-benzene,
(I.4)	

	2-(4-ethylbenzyl)-4-(β -D-glucopyranos-1-yl)-5-hydroxy-benzonitrile,
(I.5)	 2-(4-ethyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzonitrile,
(I.6)	 2-(4-cyclopropyl-benzyl)-4-(β-D-glucopyranos-1-yl)-benzonitrile,
(I.7)	 1-chloro-4-(β-D-glucopyranos-1-yl)-2-(4-ethynyl-benzyl)-benzene,
(I.8)	 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((<i>R</i>)-tetrahydrofuran-3-yloxy)-benzyl]-benzene,
(I.9)	 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((<i>S</i>)-tetrahydrofuran-3-yloxy)-

	benzyl]-benzene,
(I.10)	 1-methyl-2-[4-((<i>R</i>)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β-D-glucopyranos-1-yl)-benzene,
(I.11)	 1-methyl-2-[4-((<i>S</i>)-tetrahydrofuran-3-yloxy)-benzyl]-4-(β-D-glucopyranos-1-yl)-benzene.

According an embodiment of the present invention the SGLT2 inhibitor is selected from the **group G1a** consisting of compounds of the beforementioned formula (I). Even more preferably the group G1a consists of glucopyranosyl-substituted benzene derivatives of the formula (I) which are selected from the compounds (I.6), (I.7), (I.8), (I.9) and (I.11). An preferred example of a SGLT2 inhibitor according to the group G1a is the compound (I.9).

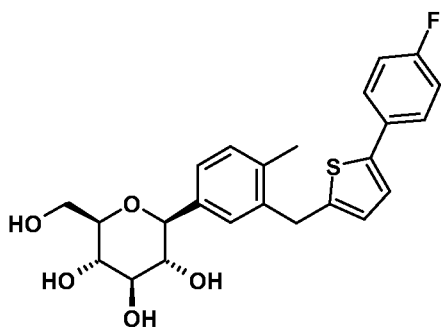
According to another embodiment of the present invention the SGLT2 inhibitor is selected from the group consisting of dapagliflozin, canagliflozin, atigliflozin, ipragliflozin and tofogliflozin.

According to this invention, it is to be understood that the definitions of the above listed SGLT2 inhibitors, including the glucopyranosyl-substituted benzene derivatives of the formula (I), also comprise their hydrates, solvates and polymorphic forms thereof, and prodrugs thereof. With regard to the preferred compound (I.7) an advantageous crystalline form is described in the international patent application WO 2007/028814 which hereby is incorporated herein in its entirety. With regard to the preferred compound (I.8), an advantageous crystalline form is described in the international patent application WO 2006/117360 which hereby is incorporated herein in its entirety. With regard to the preferred compound (I.9) an advantageous crystalline form is described in the international patent

application WO 2006/117359 which hereby is incorporated herein in its entirety. With regard to the preferred compound (I.11) an advantageous crystalline form is described in the international patent application WO 2008/049923 which hereby is incorporated herein in its entirety. These crystalline forms possess good solubility properties which enable a good bioavailability of the SGLT2 inhibitor. Furthermore, the crystalline forms are physico-chemically stable and thus provide a good shelf-life stability of the pharmaceutical composition.

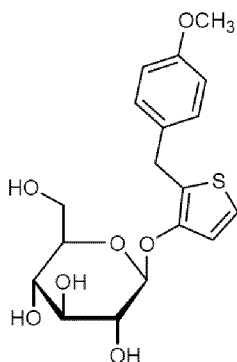
The term "dapagliflozin" as employed herein refers to dapagliflozin, including hydrates and solvates thereof, and crystalline forms thereof. The compound and methods of its synthesis are described in WO 03/099836 for example. Preferred hydrates, solvates and crystalline forms are described in the patent applications WO 2008/116179 and WO 2008/002824 for example.

The term "canagliflozin" as employed herein refers to canagliflozin, including hydrates and solvates thereof, and crystalline forms thereof and has the following structure:



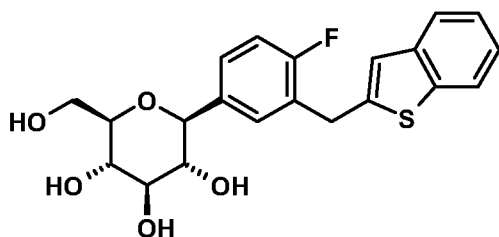
The compound and methods of its synthesis are described in WO 2005/012326 and WO 2009/035969 for example. Preferred hydrates, solvates and crystalline forms are described in the patent applications WO 2008/069327 for example.

The term "atigliflozin" as employed herein refers to atigliflozin, including hydrates and solvates thereof, and crystalline forms thereof and has the following structure:



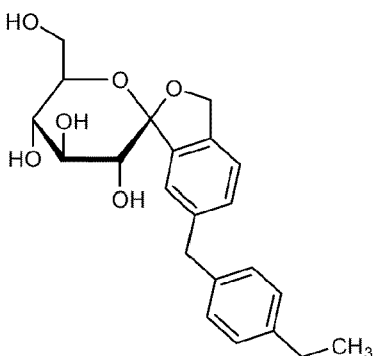
The compound and methods of its synthesis are described in WO 2004/007517 for example.

5 The term "ipragliflozin" as employed herein refers to ipragliflozin, including hydrates and solvates thereof, and crystalline forms thereof and has the following structure:



The compound and methods of its synthesis are described in WO 2004/080990, WO 2005/012326 and WO 2007/114475 for example.

10 The term "tofogliflozin" as employed herein refers to tofogliflozin, including hydrates and solvates thereof, and crystalline forms thereof and has the following structure:



The compound and methods of its synthesis are described in WO 2007/140191 and WO 2008/013280 for example.

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The term "remogliflozin" as employed herein refers to remogliflozin and prodrugs of remogliflozin, in particular remogliflozin etabonate, including hydrates and solvates thereof,

and crystalline forms thereof. Methods of its synthesis are described in the patent applications EP 1213296 and EP 1354888 for example.

5 The term "sergliflozin" as employed herein refers to sergliflozin and prodrugs of sergliflozin, in particular sergliflozin etabonate, including hydrates and solvates thereof, and crystalline forms thereof. Methods for its manufacture are described in the patent applications EP 1344780 and EP 1489089 for example.

10 For avoidance of any doubt, the disclosure of each of the foregoing documents cited above in connection with the specified SGLT2 inhibitors is specifically incorporated herein by reference in its entirety.

The aspects according to the present invention, in particular the pharmaceutical compositions, methods and uses, refer to an insulin, which includes normal insulin, human 15 insulin, insulin derivatives, zinc insulins and insulin analogues, including formulations thereof with modified release profiles. in particular as used in the therapy of humans. The insulin may be selected from the group consisting of:

- rapid-acting insulins,
- short-acting insulins,
- 20 - intermediate-acting insulins,
- long-acting insulins,
- and mixtures thereof.

25 Mixtures of insulins may comprise mixtures of short- or rapid-acting insulins with long-acting insulins. For example such mixtures are marketed as Actraphane/Mixtard or Novomix.

The term "insulin" in the scope of the present invention covers insulins as described hereinbefore and hereinafter which are administered to the patient via injection, preferably subcutaneous injection, via infusion, including pumps, via inhalation or other routes of 30 administration. Insulins to be administered via inhalation are for example Exubera (Pfizer), AIR (Lilly) and AER (Novo Nordisk).

Rapid-acting insulins usually start lowering the blood glucose within about 5 to 15 minutes and are effective for about 3 to 4 hours. Examples of rapid-acting insulins are insulin aspart, 35 insulin lispro and insulin glulisine. Insulin Lispro is marketed under the trade name Humalog

and Liprolog. Insulin Aspart is marketed under the trade names NovoLog and NovoRapid. Insulin glulisine is marketed under the trade name Apidra.

5 Short-acting insulins usually start lowering the blood glucose within about 30 minutes and are effective about 5 to 8 hours. An example is regular insulin or human insulin.

10 Intermediate-acting insulins usually start lowering the blood glucose within about 1 to 3 hours and are effective for about 16 to 24 hours. An example is NPH insulin, also known as Humulin N, Novolin N, Novolin NPH and isophane insulin. Another example are lente insulins, such as Semilente or Monotard.

15 Long-acting insulins usually start lowering the blood glucose within 1 to 6 hours and are effective for up to about 24 hours or even up to or beyond 32 hours. Long-acting insulin usually provides a continuous level of insulin activity (for up to 24-36 hours) and usually operates at a maximum strength (with flat action profile) after about 8-12 hours, sometimes longer. Long-acting insulin is usually administered in the morning or before bed. Examples of long-acting insulin may include, but are not limited to, insulin glargine, insulin detemir or insulin degludec, which are insulin analogues, and ultralente insulin, which is regular human insulin formulated for slow absorption. Long-acting insulin is suited to provide for basal, as
20 opposed to prandial, insulin requirements (e.g. to control hyperglycemia). Long-acting insulin may be typically administered ranging from twice or once daily, over thrice weekly up to once weekly (ultra long-acting insulin). Insulin glargine is marketed under the trade name Lantus for example. Insulin detemir is marketed under the tradename Levemir for example.

25 In one embodiment, the long-acting insulin of this invention refers to any insulin known in the art which is used for a basal insulin therapy and which have a basal release profile. A basal release profile refers to the kinetic, amount and rate of release of the insulin from the formulation into a patient's systemic circulation. In a graph of the patient's mean plasma insulin levels over time, a basal release profile typically has a minimal peak (often referred to as "a peakless profile" or "flat profile") and slowly and continuously releases insulin for a
30 prolonged period of time.

In a further embodiment, the long-acting insulin is an acylated derivative of human insulin. Acylated insulin derivatives may be such wherein a lipophilic group is attached to the lysine
35 residue in position B29. A commercial product is Levemir® comprising Lys^{B29}(N^ε-

tetradecanoyl) des(B30) human insulin (insulin detemir). Another example is $N^{\epsilon B29}-(N^{\alpha}-(\omega$ -carboxypentadecanoyl)-L- γ -glutamyl) des(B30) human insulin (insulin degludec).

5 In a further embodiment, the long-acting insulin is such comprising positively charged amino acids such as Arg attached to the C-terminal end of the B-chain. A commercial product is Lantus[®] (insulin glargine) comprising Gly^{A21}, Arg^{B31}, Arg^{B32} human insulin.

According to one embodiment of the invention the insulin is selected from the group consisting of long acting insulins.

10

According to another embodiment the insulin is selected from the **group G2** consisting of the long acting insulins (L1) to (L7) as described hereinafter:

(L1): Insulin glargine

15 Insulin glargine (marketed as LANTUS[®] by Sanofi-Aventis) is approved and marketed for subcutaneous administration once a day. Insulin glargine provides relatively constant glucose lowering activity over a 24-hour period and may be administered any time during the day provided it is administered at the same time every day.

20 (L2): Insulin detemir

Insulin detemir (marketed as LEVEMIR[®] by Novo Nordisk) is approved and marketed for subcutaneous administration either twice a day or once a day, preferably with the evening meal or at bedtime.

25 (L3): Insulin degludec

Insulin degludec (NN1250) is a neutral, soluble ultra-long acting insulin with a duration of action more than 24 hours. Degludec has a very flat, predictable and smooth action profile. It is intended for subcutaneous administration once daily or less (e.g. three times a week).

30 (L4): Insulin lispro PEGylated

Insulin lispro PEGylated with high molecular weight poly(ethylene glycol) derivatives especially as disclosed in WO 2009/152128 (the disclosure of which is incorporated herein), such as e.g. the PEGylated insulin lispro compound of the formula P-[(A)-(B)], or a pharmaceutically acceptable salt thereof, wherein A is the A-chain of insulin lispro, B is the B-chain of insulin lispro, and P is a PEG having a molecular weight in the range from about

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17,5 kDa to about 40 kDa, and wherein A and B are properly cross-linked and P is attached via a urethane covalent bond to the epsilon-amino group of the lysine at position 28 of B.

(L5): Amidated insulin glargine

- 5 Amidated insulin glargine especially in the form of Gly^{A21}, Arg^{B31}, Arg^{B32}-NH₂ human insulin (insulin glargine amide, i.e. the C-terminus of the B-chain of insulin glargine is amidated) as disclosed in WO 2008/006496 or WO 2008/006496 (the disclosures of which are incorporated herein).

10 (L6):

Lys^{B29}(N^ε-lithocholyl-γ-Glu) des(B30) human insulin or N^{εB29}-ω-carboxypentadecanoyl-γ-amino-butanoyl des(B30) human insulin.

(L7):

- 15 Amidated insulin analogs as disclosed in WO 2009/087082 (the disclosure of which is incorporated herein), especially one selected from claim 14, or in WO 2009/087081 (the disclosure of which is incorporated herein), especially one selected from claim 16.

Preferred members of the group G2 are L1, L2 and L3, in particular insulin glargine.

20

Long-acting insulins analogues are typically given as basic anti-diabetic therapy to type 1 diabetes, type 2 diabetes or latent autoimmune diabetes with onset in adults (LADA) patients to control the blood sugar when no food intake occurs. As mentioned above, this type of insulin provides a continuous level of insulin activity for up to 36 hours. Long-acting insulin operates at maximum strength after about 8-12 hours. Because of their advantages, it is thought that treatment with these insulin analogues can lead to a beneficial effect, for example less hypoglycaemia, less weight gain or a better metabolic control possibly resulting in less late diabetic complications such as problems with eyes, kidneys or feet and myocardial infarction, stroke or death.

30

According to the invention, there are provided methods for treating a patient with regard to diseases and conditions as described hereinbefore and hereinafter characterized in that an SGLT2 inhibitor and an insulin are administered, for example in combination or alternation, to the patient. Said diseases and conditions comprise diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, diseases which require treatment with insulin, conditions

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which require treatment with insulin, inter alia. According to one embodiment of the invention the insulin is part of a basal insulin therapy.

The term basal insulin therapy relates to a therapy in which one or more insulins are administered to a patient such that in a graph of the patient's mean plasma insulin levels over time, a basal release profile typically has a minimal peak (often referred to as "a peakless profile" or "flat profile") and slowly and continuously releases insulin for a prolonged period of time. According to one embodiment the basal insulin therapy includes the administration of a long-acting insulins to a patient. According to another embodiment the basal insulin therapy includes the administration of an insulin, in particular a rapid-acting or short-acting insulin, including human insulin, to a patient via infusion, for example via a pump in order to achieve the desired patient's mean plasma insulin level for a prolonged period of time, for example over 12 or 24 hours or longer.

Therefore according to one embodiment of the invention there is provided a method for treating a disease or condition selected from the group consisting of diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus and a disease or condition which requires treatment with insulin in a patient characterized in that the patient receives a basal insulin therapy and in addition a SGLT2 inhibitor is administered to the patient.

According to one aspect of this embodiment the patient receives a basal insulin therapy wherein a long-acting insulin is administered to the patient. For example the long-acting insulin is administered via injection, for example subcutaneous injection. Preferably the SGLT2 inhibitor is administered orally. According to this aspect the long-acting insulin and the SGLT2 inhibitor are administered in combination or alternation, i.e. at the same time or at different times. For example the long-acting insulin is administered to the patient once or twice, preferably once daily. For example the SGLT2 inhibitor is administered to the patient once or twice, preferably once daily.

According to another aspect of this embodiment the patient receives a basal insulin therapy wherein an insulin is administered to the patient via infusion, for example via a pump. According to this aspect the insulin may be a rapid-acting or short-acting insulin, for example a human insulin. Preferably the SGLT2 inhibitor is administered orally. According to this aspect the insulin and the SGLT2 inhibitor are administered in combination or alternation, i.e. at the same time or at different times. For example the insulin is administered to the patient several times daily via pump infusion wherein the time and dose are chosen in order to

achieve a certain range of plasma insulin level. For example the SGLT2 inhibitor is administered to the patient once or twice, preferably once daily.

According to another embodiment of the present invention the pharmaceutical composition,
5 the methods and uses according to the invention additionally comprise a further antidiabetic agent.

A further antidiabetic agent is selected from the **group G3** consisting of biguanides, thiazolidindiones, sulfonylureas, glinides, inhibitors of alpha-glucosidase, GLP-1 analogues,
10 DPP-4 inhibitors and amylin analogs, including pharmaceutically acceptable salts of the beforementioned agents. In the following preferred embodiments regarding the third antidiabetic agent are described.

The group G3 comprises biguanides. Examples of biguanides are metformin, phenformin
15 and buformin. A preferred biguanide is metformin.

The term "metformin" as employed herein refers to metformin or a pharmaceutically acceptable salt thereof such as the hydrochloride salt, the metformin (2:1) fumarate salt, and the metformin (2:1) succinate salt, the hydrobromide salt, the p-chlorophenoxy acetate or the
20 embonate, and other known metformin salts of mono and dibasic carboxylic acids. It is preferred that the metformin employed herein is the metformin hydrochloride salt.

The group G3 comprises thiazolidindiones. Examples of thiazolidindiones (TZD) are pioglitazone and rosiglitazone.
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The term "pioglitazone" as employed herein refers to pioglitazone, including its enantiomers, mixtures thereof and its racemate, or a pharmaceutically acceptable salt thereof such as the hydrochloride salt.

30 The term "rosiglitazone" as employed herein refers to rosiglitazone, including its enantiomers, mixtures thereof and its racemate, or a pharmaceutically acceptable salt thereof such as the maleate salt.

The group G3 comprises sulfonylureas. Examples of sulfonylureas are glibenclamide,
35 tolbutamide, glimepiride, glipizide, gliquidone, glibornuride, glyburide, glisoxepide and

gliclazide. Preferred sulfonylureas are tolbutamide, gliquidone, glibenclamide, glipizide and glimepiride, in particular glibenclamide, glipizide and glimepiride.

Each term of the group "glibenclamide", "glimepiride", "gliquidone", "glibornuride",
5 "gliclazide", "glisoxepide", "tolbutamide" and "glipizide" as employed herein refers to the respective active drug or a pharmaceutically acceptable salt thereof.

The group G3 comprises glinides. Examples of glinides are nateglinide, repaglinide and mitiglinide.

10

The term "nateglinide" as employed herein refers to nateglinide, including its enantiomers, mixtures thereof and its racemate, or a pharmaceutically acceptable salts and esters thereof.

The term "repaglinide" as employed herein refers to repaglinide, including its enantiomers,
15 mixtures thereof and its racemate, or a pharmaceutically acceptable salts and esters thereof.

The group G3 comprises inhibitors of alpha-glucosidase. Examples of inhibitors of alpha-glucosidase are acarbose, voglibose and miglitol.

20 Each term of the group "acarbose", "voglibose" and "miglitol" as employed herein refers to the respective active drug or a pharmaceutically acceptable salt thereof.

The group G3 comprises inhibitors of GLP-1 analogues. Examples of GLP-1 analogues are exenatide and liraglutide.

25

Each term of the group "exenatide" and "liraglutide" as employed herein refers to the respective active drug or a pharmaceutically acceptable salt thereof.

The group G3 comprises inhibitors of DPP-4 inhibitors. Examples of DPP-4 inhibitors are
30 linagliptin, sitagliptin, vildagliptin, saxagliptin, denagliptin, alogliptin, carmegliptin, melogliptin, dutogliptin, including pharmaceutically acceptable salts thereof, hydrates and solvates thereof.

The group G3 comprises amylin analogs. An example of an amylin analog is pramlintide,
35 including pharmaceutically acceptable salts thereof, hydrates and solvates thereof. For example pramlintide acetate is marketed under the tradename Symlin.

According to an embodiment the pharmaceutical compositions, methods and uses according to the present invention relate to a combination of a SGLT2 inhibitor and an insulin which is preferably selected from the group of sub-embodiments E1 to E36 according to the entries in the Table 1.

5

Table 1

Embodiment	SGLT2 Inhibitor	Insulin
E1	selected from the group G1	insulin
E2	selected from the group G1	rapid-acting or short-acting insulin
E3	selected from the group G1	human insulin
E4	selected from the group G1	intermediate-acting or long-acting insulin
E5	selected from the group G1	long-acting insulin
E6	selected from the group G1	selected from the group G2
E7	selected from the group G1	L1
E8	selected from the group G1	L2
E9	selected from the group G1	L3
E10	selected from the group G1	L4
E11	selected from the group G1	L5
E12	selected from the group G1	L6
E13	selected from the group G1	L7
E14	selected from the group G1a	insulin
E15	selected from the group G1a	rapid-acting or short-acting insulin
E16	selected from the group G1a	human insulin
E17	selected from the group G1a	intermediate-acting or long-acting insulin
E18	selected from the group G1a	long-acting insulin
E19	selected from the group G1a	selected from the group G2
E20	selected from the group G1a	L1
E21	selected from the group G1a	L2
E22	selected from the group G1a	L3
E23	selected from the group G1a	L4
E24	selected from the group G1a	L5
E25	selected from the group G1a	L6

E26	selected from the group G1a	L7
E27	Compound (I.9)	insulin
E28	Compound (I.9)	rapid-acting or short-acting insulin
E29	Compound (I.9)	human insulin
E30	Compound (I.9)	intermediate-acting or long-acting insulin
E31	Compound (I.9)	long-acting insulin
E32	Compound (I.9)	selected from the group G2
E33	Compound (I.9)	L1
E34	Compound (I.9)	L2
E35	Compound (I.9)	L3
E36	Compound (I.9)	L4
E37	Compound (I.9)	L5
E38	Compound (I.9)	L6
E39	Compound (I.9)	L7

Among the combinations according to the present invention listed in Table 1, the combination according to the entries E27 to E39 are even more preferred.

- 5 According to a further embodiment the pharmaceutical compositions, methods and uses according to the present invention relate to a combination of a SGLT2 inhibitor and an insulin which additionally comprises a further antidiabetic agent. Preferred sub-embodiments are selected from the entries F1 to F72 in the Table 2.

10 Table 2

Embo-diment	SGLT2 Inhibitor	Insulin	Further antidiabetic agent
F1	selected from the group G1	insulin	metformin
F2	selected from the group G1	rapid-acting or short-acting insulin	metformin
F3	selected from the group G1	human insulin	metformin
F4	selected from the group G1	intermediate-acting or long-acting insulin	metformin
F5	selected from the group G1	selected from the group G2	metformin

F6	selected from the group G1a	insulin	metformin
F7	selected from the group G1a	rapid-acting or short-acting insulin	metformin
F8	selected from the group G1a	human insulin	metformin
F9	selected from the group G1a	intermediate-acting or long-acting insulin	metformin
F10	selected from the group G1a	long-acting insulin	metformin
F11	selected from the group G1a	selected from the group G2	metformin
F12	Compound (I.9)	insulin	metformin
F13	Compound (I.9)	rapid-acting or short-acting insulin	metformin
F14	Compound (I.9)	human insulin	metformin
F15	Compound (I.9)	intermediate-acting or long-acting insulin	metformin
F16	Compound (I.9)	long-acting insulin	metformin
F17	Compound (I.9)	selected from the group G2	metformin
F18	Compound (I.9)	L1	metformin
F19	Compound (I.9)	L2	metformin
F20	Compound (I.9)	L3	metformin
F21	Compound (I.9)	L4	metformin
F22	Compound (I.9)	L5	metformin
F23	Compound (I.9)	L6	metformin
F24	Compound (I.9)	L7	metformin
F25	selected from the group G1	insulin	pioglitazone
F26	selected from the group G1	rapid-acting or short-acting insulin	pioglitazone
F27	selected from the group G1	human insulin	pioglitazone
F28	selected from the group G1	intermediate-acting or long-acting insulin	pioglitazone
F29	selected from the group G1	selected from the group G2	pioglitazone
F30	selected from the group G1a	insulin	pioglitazone

F31	selected from the group G1a	rapid-acting or short-acting insulin	pioglitazone
F32	selected from the group G1a	human insulin	pioglitazone
F33	selected from the group G1a	intermediate-acting or long-acting insulin	pioglitazone
F34	selected from the group G1a	long-acting insulin	pioglitazone
F35	selected from the group G1a	selected from the group G2	pioglitazone
F36	Compound (I.9)	insulin	pioglitazone
F37	Compound (I.9)	rapid-acting or short-acting insulin	pioglitazone
F38	Compound (I.9)	human insulin	pioglitazone
F39	Compound (I.9)	intermediate-acting or long-acting insulin	pioglitazone
F40	Compound (I.9)	long-acting insulin	pioglitazone
F41	Compound (I.9)	selected from the group G2	pioglitazone
F42	Compound (I.9)	L1	pioglitazone
F43	Compound (I.9)	L2	pioglitazone
F44	Compound (I.9)	L3	pioglitazone
F45	Compound (I.9)	L4	pioglitazone
F46	Compound (I.9)	L5	pioglitazone
F47	Compound (I.9)	L6	pioglitazone
F48	Compound (I.9)	L7	pioglitazone
F49	selected from the group G1	insulin	linagliptin
F50	selected from the group G1	rapid-acting or short-acting insulin	linagliptin
F51	selected from the group G1	human insulin	linagliptin
F52	selected from the group G1	intermediate-acting or long-acting insulin	linagliptin
F53	selected from the group G1	selected from the group G2	linagliptin
F54	selected from the group G1a	insulin	linagliptin
F55	selected from the group G1a	rapid-acting or short-acting insulin	linagliptin

F56	selected from the group G1a	human insulin	linagliptin
F57	selected from the group G1a	intermediate-acting or long-acting insulin	linagliptin
F58	selected from the group G1a	long-acting insulin	linagliptin
F59	selected from the group G1a	selected from the group G2	linagliptin
F60	Compound (I.9)	insulin	linagliptin
F61	Compound (I.9)	rapid-acting or short-acting insulin	linagliptin
F62	Compound (I.9)	human insulin	linagliptin
F63	Compound (I.9)	intermediate-acting or long-acting insulin	linagliptin
F64	Compound (I.9)	long-acting insulin	linagliptin
F65	Compound (I.9)	selected from the group G2	linagliptin
F66	Compound (I.9)	L1	linagliptin
F67	Compound (I.9)	L2	linagliptin
F68	Compound (I.9)	L3	linagliptin
F69	Compound (I.9)	L4	linagliptin
F70	Compound (I.9)	L5	linagliptin
F71	Compound (I.9)	L6	linagliptin
F72	Compound (I.9)	L7	linagliptin

The combination of an SGLT2 inhibitor and an insulin according to this invention significantly improves the glycemic control, in particular in patients as described hereinafter, compared with a monotherapy using either a SGLT2 inhibitor or an insulin alone, for example with a monotherapy of a long-acting insulin, such as insulin glargine. Furthermore the combination of an SGLT2 inhibitor and an insulin according to this invention allows a reduction of the dose of the insulin compared with a monotherapy of said insulin, for example with a monotherapy of a long-acting insulin, such as insulin glargine. With a reduction of the dose of the insulin any side effects associated with the therapy using said insulin may be prevented or attenuated. A dose reduction is beneficial for patients which otherwise would potentially suffer from side effects in a therapy using a higher dose of one or more of the active ingredients, in particular with regard to side effect caused by the insulin. Therefore, the pharmaceutical composition as well as the methods according to the present invention, show less side effects, thereby making the therapy more tolerable and improving the patients

compliance with the treatment. In addition the efficacy of the insulin, for example in a basal insulin therapy with a long acting insulin or with a short- or rapid acting insulin, including human insulin, via infusion with a pump, may be prolonged by a combined treatment with a SGLT-2 inhibitor. Therefore the time interval between two applications, for example subcutaneous injections or infusions via a pump, of the insulin may be prolonged. For example in a combination therapy employing a long acting insulin and a SGLT2 inhibitor according to the invention the dose of the long acting insulin, the dose of the SGLT2 inhibitor, the time intervall between two applications of the long acting insulin and the time intervall between the application of the long acting insulin and the SGLT2 inhibitor are chosen such that a good glycemic control is provided to the patient for a given time period, in particular for 24 hours.

When this invention refers to patients requiring treatment or prevention, it relates primarily to treatment and prevention in humans, but the pharmaceutical composition may also be used accordingly in veterinary medicine in mammals. In the scope of this invention the term "patient" covers adult humans (age of 18 years or older), adolescent humans (age 10 to 17 years) and children (age 6-9 years).

Furthermore, the method and/or use according to this invention is advantageously applicable in those patients who show one, two or more of the following conditions:

- (a) type 1 diabetes mellitus;
- (b) need for treatment with insulin;
- (c) latent autoimmune diabetes with onset in adults (LADA).

Furthermore, the method and/or use according to this invention is advantageously applicable in those patients who are or shall be treated with a insulin, for example with insulin glargine or detemir insulin, in particular in patients diagnosed with type 1 diabetes mellitus, and show one, two or more of the following conditions, including the risk to develop such conditions:

- (d) nocturnal and/or early morning hypoglycemia;
- (e) hypoglycemic episodes;
- (f) hyperglycemic episodes;
- (g) cardiac or cerebral complications;
- (h) retinopathy, in particular proliferative retinopathy;
- (i) injection site reactions, for example skin or subcutaneous tissue disorders.

As described hereinbefore by the administration of the pharmaceutical composition according to this invention and in particular in view of the high SGLT2 inhibitory activity of the SGLT2 inhibitors therein, excessive blood glucose is excreted through the urine of the patient, so that less or no gain in weight or even a reduction in body weight may result.

5 Therefore, a treatment or prophylaxis according to this invention is advantageously suitable in those patients in need of such treatment or prophylaxis who are diagnosed of one or more of the conditions selected from the group consisting of overweight and obesity, in particular class I obesity, class II obesity, class III obesity, visceral obesity and abdominal obesity. In addition a treatment or prophylaxis according to this invention is advantageously suitable in
10 those patients in which a weight increase is contraindicated. Any weight increasing effect in the therapy, for example due to the administration of the third antidiabetic agent, may be attenuated or even avoided thereby.

Therefore, according to a preferred embodiment of the present invention, there is provided a
15 method for improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c in a patient in need thereof who is diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG) with insulin resistance, with metabolic syndrome and/or with type 1 diabetes mellitus or type 2 diabetes mellitus characterized in that an SGLT2 inhibitor and an insulin as
20 defined hereinbefore and hereinafter are administered, for example in combination or alternation, to the patient.

According to another preferred embodiment of the present invention, there is provided a method for improving glycemic control in patients, in particular in adult patients, with type 1 or
25 type 2 diabetes mellitus as an adjunct to diet and exercise.

It can be found that by using a pharmaceutical composition according to this invention, an improvement of the glycemic control can be achieved even in those patients who have insufficient glycemic control in particular despite treatment with an insulin, for example
30 despite maximal recommended or tolerated dose of monotherapy with the insulin.

Furthermore, the pharmaceutical composition, the methods and uses according to this invention are particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions

- 35 (a) obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,
(b) triglyceride blood level ≥ 150 mg/dL,

- (c) HDL-cholesterol blood level < 40 mg/dL in female patients and < 50 mg/dL in male patients,
- (d) a systolic blood pressure $\geq$ 130 mm Hg and a diastolic blood pressure $\geq$ 85 mm Hg,
- (e) a fasting blood glucose level $\geq$ 100 mg/dL.

5

It is assumed that patients diagnosed with impaired glucose tolerance (IGT), impaired fasting blood glucose (IFG), with insulin resistance and/or with metabolic syndrome suffer from an increased risk of developing a cardiovascular disease, such as for example myocardial infarction, coronary heart disease, heart insufficiency, thromboembolic events. A glycemic control according to this invention may result in a reduction of the cardiovascular risks.

10

Furthermore, the pharmaceutical composition, the methods and uses according to this invention are particularly suitable in the treatment of patients after organ transplantation, in particular those patients who are diagnosed having one or more of the following conditions

15

- (a) a higher age, in particular above 50 years,
- (b) male gender;
- (c) overweight, obesity (including class I, II and/or III obesity), visceral obesity and/or abdominal obesity,
- (d) pre-transplant diabetes,
- (e) immunosuppression therapy.

20

Furthermore, the pharmaceutical composition, the methods and the uses according to this invention are particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions:

25

- (a) hyponatremia, in particular chronic hyponatremia;
- (b) water intoxication;
- (c) water retention;
- (d) plasma sodium concentration below 135 mmol/L.

30

Furthermore, the pharmaceutical composition, the methods and uses according to this invention are particularly suitable in the treatment of patients who are diagnosed having one or more of the following conditions:

- (a) high serum uric acid levels, in particular greater than 6.0 mg/dL (357 μ mol/L);
- (b) a history of gouty arthritis, in particular recurrent gouty arthritis;
- (c) kidney stones, in particular recurrent kidney stones;
- (d) a high propensity for kidney stone formation.

35

A pharmaceutical composition according to this invention, in particular due to the SGLT2 inhibitor exhibits a good safety profile. Therefore, a treatment according to this invention is advantageous in those patients for which a reduction of the dose of the insulin is

5 recommended.

A pharmaceutical composition according to this invention is particularly suitable in the long term treatment or prophylaxis of the diseases and/or conditions as described hereinbefore and hereinafter, in particular in the long term glycemic control in patients with type 1 diabetes mellitus or type 2 diabetes mellitus.

10

The term "long term" as used hereinbefore and hereinafter indicates a treatment of or administration in a patient within a period of time longer than 12 weeks, preferably longer than 25 weeks, even more preferably longer than 1 year.

15

Therefore, a particularly preferred embodiment of the present invention provides a method for therapy, preferably oral therapy, for improvement, especially long term improvement, of glycemic control in patients with type 1 diabetes mellitus.

20 Therefore, a particularly preferred embodiment of the present invention provides a method for therapy, preferably oral therapy, for improvement, especially long term improvement, of glycemic control in patients with type 2 diabetes mellitus, especially in patients with late stage type 2 diabetes mellitus, in particular in patients additionally diagnosed of overweight, obesity (including class I, class II and/or class III obesity), visceral obesity and/or abdominal

25 obesity.

Unless otherwise noted, the combination therapy according to the invention may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy.

30

According to one embodiment the SGLT2 inhibitor and the insulin and optionally the further antidiabetic agent are administered in combination, i.e. simultaneously, for example in one single formulation or in two separate formulations or dosage forms, or in alternation, for example successively in two or three separate formulations or dosage forms. Hence, the administration of one combination partner, i.e. the SGLT2 inhibitor or the insulin, may be

35 prior to, concurrent to, or subsequent to the administration of the other combination partner.

In one embodiment, for the combination therapy according to this invention the SGLT2 inhibitor and the insulin are administered in different formulations or different dosage forms. In another embodiment, for the combination therapy according to this invention the SGLT2 inhibitor and the insulin are administered in the same formulation or in the same dosage form.

Therefore according to an embodiment of the present invention there is provided a pharmaceutical composition or fixed dose combination comprising

a) a SGLT2 inhibitor as defined herein, and

b) an insulin as defined herein,

and, optionally, one or more pharmaceutically acceptable carriers and/or diluents.

Within the scope of the present invention, the SGLT2 inhibitor is preferably administered orally or by injection, preferably orally. The insulin is preferably administered by injection, preferably subcutaneously, or by infusion, for example with a pump. Other forms of administration are possible and described hereinafter. Preferably the optionally administered other antidiabetic agent is administered orally. In this case the SGLT2 inhibitor and the other antidiabetic agent may be comprised together in one dosage form or in separate dosage forms.

Therefore according to another embodiment the present invention provides a pharmaceutical composition, delivery system or device for systemic use, in particular for administration by injection or infusion, for example subcutaneous injection or infusion via pump, comprising

a) a SGLT2 inhibitor as defined herein, and, optionally,

b) an insulin as defined herein,

and, optionally, one or more pharmaceutically acceptable carriers and/or diluents.

It will be appreciated that the amount of the SGLT2 inhibitor and the insulin and optionally of the further antidiabetic agent according to this invention to be administered to the patient and required for use in treatment or prophylaxis according to the present invention will vary with the route of administration, the nature and severity of the condition for which treatment or prophylaxis is required, the age, weight and condition of the patient, concomitant medication and will be ultimately at the discretion of the attendant physician. In general, however, the SGLT2 inhibitor, the insulin and optionally the further antidiabetic agent according to this invention are included in the pharmaceutical composition or dosage form in an amount

sufficient that by their administration in combination and/or alternation the glycemic control in the patient to be treated is improved.

For the treatment of hyperuricemia or hyperuricemia associated conditions the SGLT2

5 inhibitor according to this invention is included in the pharmaceutical composition or dosage form in an amount sufficient that is sufficient to treat hyperuricemia without disturbing the patient's plasma glucose homeostasis, in particular without inducing hypoglycemia.

For the treatment or prevention of kidney stones the SGLT2 inhibitor according to this

10 invention is included in the pharmaceutical composition or dosage form in an amount sufficient that is sufficient to treat or prevent kidney stones without disturbing the patient's plasma glucose homeostasis, in particular without inducing hypoglycemia.

For the treatment of hyponatremia and associated conditions the SGLT2 inhibitor according to this invention is included in the pharmaceutical composition or dosage form in an amount

15 sufficient that is sufficient to treat hyponatremia or the associated conditions without disturbing the patient's plasma glucose homeostasis, in particular without inducing hypoglycemia.

20 In the following preferred ranges of the amount of the SGLT2 inhibitor, the insulin and optionally the further antidiabetic agent to be employed in the pharmaceutical composition and the methods and uses according to this invention are described. These ranges refer to the amounts to be administered per day with respect to an adult patient, in particular to a human being, for example of approximately 70 kg body weight, and can be adapted

25 accordingly with regard to an administration 1 or 2 times daily and with regard to other routes of administration and with regard to the age of the patient. The ranges of the dosage and amounts are calculated for the individual active moiety. Advantageously, the combination therapy according to the present invention utilizes lower dosages of the individual SGLT2 inhibitor, of the individual insulin and/or optionally of the individual further antidiabetic agent

30 used in monotherapy or used in conventional therapeutics, thus avoiding possible adverse side effects incurred when those agents are used as monotherapies.

In general, the amount of the SGLT2 inhibitor in the pharmaceutical composition, methods and uses according to this invention is preferably in the range from 1/5 to 1/1 of the amount

35 usually recommended for a monotherapy using said SGLT2 inhibitor.

The preferred dosage range of the SGLT2 inhibitor is in the range from 0.5 mg to 200 mg, even more preferably from 1 to 100 mg, most preferably from 1 to 50 mg per day. The oral administration is preferred. Therefore, a pharmaceutical composition may comprise the hereinbefore mentioned amounts, in particular from 1 to 50 mg or 1 to 25 mg. Particular dosage strengths (e.g. per tablet or capsule) are for example 1, 2.5, 5, 7.5, 10, 12.5, 15, 20, 25 or 50 mg of the compound of the formula (I), in particular of the compound (I.9), or of dapagliflozin. The application of the active ingredient may occur one, two or three times a day, preferably once a day.

- 10 In general, the amount of the insulin in the pharmaceutical composition, methods and uses according to this invention is preferably in the range from 1/5 to 1/1 of the amount usually recommended for a monotherapy using said long acting insulin.

15 The insulin is typically administered by subcutaneous injection, e.g. ranging from twice daily, once daily to once weekly injection. Suitable doses and dosage forms of the insulin may be determined by a person skilled in the art. Blood glucose monitoring is essential in all patients receiving insulin therapy. Doses of a long-acting insulin will be individualized according to the response to treatment and obtainment of glycaemic control. Doses are; typically in the range of 10 to 70 units/day. According to the WHO the defined daily dose of 20 insulin is 40 units. Usually long acting insulins are given once daily, either in the morning or in the evening. An SGLT-2 inhibitor could be administered at any of these time points. Type 1 diabetes patients would usually be treated with a multiple daily injection regimen comprising basal insulin, for example a long-acting insulin, and a rapid acting insulin. A typical daily insulin requirement in type 1 diabetes is 40 to 60 units, depending on beta- 25 cell function, age, weight, degree of physical activity, eating and drinking. Typically around 40-60% of the total daily insulin requirement would be given as basal insulin, for example with a long-acting insulin.

For example, insulin glargine (Lantus) is administered subcutaneously once a day. Lantus 30 may be administered at any time during the day, but at the same time every day. The dose of Lantus is individualized based on clinical response. A typical starting dose of Lantus in patients with type 2 diabetes who are not currently treated with insulin is 10 units, or alternatively 0.2 U/kg, once daily, which should subsequently be adjusted to the patient's needs. Type 1 diabetes patients would usually be treated with a multiple daily 35 injection regimen comprising basal insulin and rapid acting insulin. A typical daily insulin

requirement in type 1 diabetes is 40 to 60 units, depending on beta-cell function, age, weight, degree of physical activity, eating and drinking. Typically around 40-60% of the total daily insulin requirement would be given as basal insulin; when Lantus is used, the same principle for dosing applies in type 1 diabetes as in type 2 diabetes. Also here, a titration of insulin dosages are needed based on clinical response.

Insulin detemir (Levemir) is administered subcutaneously once or twice a day. For patients treated with Levemir once daily, the dose is preferably administered with the evening meal or at bedtime. For patients who require twice-daily dosing, the evening dose can be administered either with evening meal, at bedtime, or 12 hours after the morning dose. The dose of Levemir is individualized based on clinical response. For insulin-naïve patients with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs, Levemir should be started at a dose of 0.1 to 0.2 Units/kg once-daily in the evening or 10 units once- or twice-daily, and the dose adjusted to achieve glycemic targets. In type 1 diabetes patients would usually be treated with a multiple daily injection regimen comprising basal insulin and rapid acting insulin. A typical daily insulin requirement in type 1 diabetes is 40-60 units, depending on beta-cell function, age, weight, degree of physical activity, eating and drinking. Typically around 40-60% of the total daily insulin requirement would be given as basal insulin; when Levemir is used, the same principle for dosing applies in type 1 diabetes as in type 2 diabetes. Also here, a titration of insulin dosages are needed based on clinical response.

Furthermore the long acting insulin analogues such as insulin degludec and basal insulin lispro will be developed with a final formulation of U-100 and dosing will be individually adapted for these insulins as well, both in type 1 and type 2 diabetes..

In case the SGLT-2 inhibitor and the insulin are to be combined with a further antidiabetic agent, the dose of the further antidiabetic agent is preferably in the range from 1/5 to 1/1 of the dose usually recommended for a monotherapy using said further antidiabetic agent. Using lower dosages of the individual further antidiabetic agent compared with monotherapy could avoid or minimize possible toxicity and adverse side effects incurred when those agents are used as monotherapies.

With regard to metformin as a preferred further antidiabetic agent metformin is usually given in doses varying from about 500 mg to 2000 mg up to 3000 mg per day using various dosing

regimens from about 100 mg to 500 mg or 200 mg to 850 mg (1-3 times a day), or about 300 mg to 1000 mg once, twice or thrice a day, or delayed-release metformin in doses of about 100 mg to 1000 mg or preferably 500 mg to 1000 mg once or twice a day or about 500 mg to 2000 mg once a day. Particular dosage strengths may be 250, 500, 625, 750, 850
5 and 1000 mg of metformin hydrochloride.

For children 10 to 16 years of age, the recommended starting dose of metformin is 500 mg given once daily. If this dose fails to produce adequate results, the dose may be increased to 500 mg twice daily. Further increases may be made in increments of 500 mg weekly to a
10 maximum daily dose of 2000 mg, given in divided doses (e.g. 2 or 3 divided doses). Metformin may be administered with food to decrease nausea.

With regard to pioglitazone as a preferred further antidiabetic agent a dosage of pioglitazone is usually of about 1-10 mg, 15 mg, 30 mg, or 45 mg once a day.

15 With regard to linagliptine as a preferred further antidiabetic agent a dosage of linagliptine is usually of about 1-10 mg, for example 1, 2.5, 5 or 10 mg once a day.

In the methods and uses according to the present invention the SGLT2 inhibitor and the
20 insulin are administered in combination or alternation. The term "administration in combination" means that the active ingredients are administered at the same time, i.e. simultaneously, or essentially at the same time. The term "administration in alternation" means that at first one of the two active ingredients, i.e. the SGLT2 inhibitor or the insulin, is administered and after a period of time the other active ingredient, i.e. the insulin or the
25 SGLT2 inhibitor, is administered, i.e. both active ingredients are administered sequentially. The period of time between the administration of the first and of the second active ingredient may be in the range from 1 min to 12 hours. The administration which is in combination or in alternation may be once, twice, three times or four times daily, preferably once or twice daily.

30 A pharmaceutical composition which is present as a separate or multiple dosage form, preferably as a kit of parts, is useful in combination therapy to flexibly suit the individual therapeutic needs of the patient.

According to a first embodiment a preferred kit of parts comprises

35 (a) a first containment containing a dosage form comprising the SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, and

- (b) a second containment containing a dosage form comprising the insulin and at least one pharmaceutically acceptable carrier.

According to a second embodiment a preferred kit of parts comprises

- 5 (a) a first containment containing a dosage form comprising the SGLT2 inhibitor and at least one pharmaceutically acceptable carrier, and
- (b) a second containment containing a dosage form comprising the insulin and at least one pharmaceutically acceptable carrier, and
- 10 (b) a third containment containing a dosage form comprising a further antidiabetic agent (for example metformin, pioglitazone or linagliptine) and at least one pharmaceutically acceptable carrier.

According to a third embodiment a preferred kit of parts comprises

- 15 (a) a first containment containing a dosage form comprising the SGLT2 inhibitor and a further antidiabetic agent and at least one pharmaceutically acceptable carrier, and
- (b) a second containment containing a dosage form comprising the insulin and at least one pharmaceutically acceptable carrier.

20 A further aspect of the present invention is a manufacture comprising the pharmaceutical composition being present as separate dosage forms according to the present invention and a label or package insert comprising instructions that the separate dosage forms are to be administered in combination or alternation.

25 According to a first embodiment a manufacture comprises (a) a pharmaceutical composition comprising a SGLT2 inhibitor according to the present invention and (b) a label or package insert which comprises instructions that the medicament may or is to be administered, for example in combination or alternation, with a medicament comprising an insulin according to the present invention or with a medicament comprising both a insulin and a further antidiabetic agent according to the present invention.

30

According to a second embodiment a manufacture comprises (a) a pharmaceutical composition comprising an insulin according to the present invention and (b) a label or package insert which comprises instructions that the medicament may or is to be administered, for example in combination or alternation, with a medicament comprising a

35 SGLT2 inhibitor according to the present invention or with a medicament comprising both a SGLT2 inhibitor and a further antidiabetic agent according to the present invention.

According to a third embodiment a manufacture comprises (a) a pharmaceutical composition comprising a SGLT2 inhibitor and a further antidiabetic agent according to the present invention and (b) a label or package insert which comprises instructions that the medicament
5 may or is to be administered, for example in combination or alternation, with a medicament comprising an insulin according to the present invention.

The desired dose of the pharmaceutical composition according to this invention may conveniently be presented in a once daily or as divided dose administered at appropriate
10 intervals, for example as two, three or more doses per day.

The pharmaceutical composition may be formulated for oral, parenteral (including sub-cutaneous) or other routes of administration in liquid or solid form. Oral administration of the SGLT2 inhibitor is preferred. The formulations may, where appropriate, be conveniently
15 presented in discrete dosage units and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the active ingredient with one or more pharmaceutically acceptable carriers, like liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired formulation. Examples of pharmaceutical compositions comprising the SGLT2 inhibitor
20 compound (I.9) are described in WO 2010/092126. Examples of pharmaceutical compositions comprising the SGLT2 inhibitor compound (I.9) and linagliptin are described in WO 2010/092124.

The pharmaceutical composition may be formulated in the form of solutions, suspensions,
25 emulsions, tablets, granules, fine granules, powders, capsules, caplets, soft capsules, pills, oral solutions, syrups, dry syrups, chewable tablets, troches, effervescent tablets, drops, fast dissolving tablets, oral fast-dispersing tablets, etc.. Preferably the pharmaceutical composition of the SGLT2 inhibitor is in the form of tablets.

The pharmaceutical composition and the dosage forms preferably comprises one or more pharmaceutical acceptable carriers. Preferred carriers must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. Examples of pharmaceutically acceptable carriers are known to the one
30 skilled in the art.

The pharmaceutical composition according to the invention may also be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Alternatively, the active ingredients may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Injectable formulations of the insulin and/or the SGLT2 inhibitor of this invention (particularly for subcutaneous use) may be prepared according to known formulation techniques, e.g. using suitable liquid carriers, which usually comprise sterile water, and, optionally, further additives such as e.g. preservatives, pH adjusting agents, buffering agents, isotoning agents, solubility aids and/or tensides or the like, to obtain injectable solutions or suspensions. In addition, injectable formulations may comprise further additives, for example salts, solubility modifying agents or precipitating agents which retard release of the drug(s). In further addition, injectable insulin formulations may comprise insulin stabilizing agents, such as zinc compounds. The component insulin of the combination according to the invention is preferably administered by injection (preferably subcutaneously) or by infusion (for example using a pump or comparable delivery system).

For further details on dosage forms, formulations and administration of SGLT2 inhibitors of this invention and/or insulin of this invention, reference is made to scientific literature and/or published patent documents, particularly to those cited herein.

The pharmaceutical compositions (or formulations) may be packaged in a variety of ways. Generally, an article for distribution includes one or more containers that contain the one or more pharmaceutical compositions in an appropriate form. Tablets are typically packed in an appropriate primary package for easy handling, distribution and storage and for assurance of proper stability of the composition at prolonged contact with the environment during storage. Primary containers for tablets may be bottles or blister packs.

Solutions for injection may be available in typical suitable presentation forms such as vials, cartridges or prefilled (disposable) pens, which may be further packaged.

The article may further comprise a label or package insert, which refers to instructions customarily included in commercial packages of therapeutic products, that may contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products. In one embodiment, the label or package inserts indicates that the composition can be used for any of the purposes described hereinbefore or hereinafter.

The pharmaceutical compositions and methods according to this invention show advantageous effects in the treatment and prevention of those diseases and conditions as described hereinbefore compared with pharmaceutical compositions and methods which comprise only one of the two active ingredients. Additional advantageous effects may be seen for example with respect to efficacy, dosage strength, dosage frequency, pharmacodynamic properties, pharmacokinetic properties, fewer adverse effects, convenience, compliance, etc..

Methods for the manufacture of SGLT2 inhibitors according to this invention and of prodrugs thereof are known to the one skilled in the art. Advantageously, the compounds according to this invention can be prepared using synthetic methods as described in the literature, including patent applications as cited hereinbefore. Preferred methods of manufacture are described in the WO 2006/120208 and WO 2007/031548. With regard to the preferred compound (I.9) an advantageous crystalline form is described in the international patent application WO 2006/117359 which hereby is incorporated herein in its entirety.

With respect to insulins the methods of synthesis are known to the skilled person and as described in the scientific literature and/ or in published patent documents, particularly in those cited hereinbefore.

The active ingredients, in particular the insulin and/or the further antidiabetic agent, may be present in the form of a pharmaceutically acceptable salt. The active ingredients or a pharmaceutically acceptable salt thereof may be present in the form of a solvate such as a hydrate or alcohol adduct.

Any of the above mentioned combinations and methods within the scope of the invention may be tested by animal models known in the art. In the following, *in vivo* experiments are described which are suitable to evaluate pharmacologically relevant properties of pharmaceutical compositions and methods according to this invention:

Pharmaceutical compositions and methods according to this invention can be tested in genetically hyperinsulinemic or diabetic animals like db/db mice, ob/ob mice, Zucker Fatty (fa/fa) rats or Zucker Diabetic Fatty (ZDF) rats. In addition, they can be tested in animals with
5 experimentally induced diabetes like HanWistar or Sprague Dawley rats pretreated with streptozotocin.

The effect on glycemic control of the combinations according to this invention can be tested after single dosing of the SGLT2 inhibitor and the insulin alone and in combination in an oral
10 glucose tolerance test in the animal models described hereinbefore. The time course of blood glucose is followed after an oral glucose challenge in overnight fasted animals. The combinations according to the present invention significantly improve glucose excursion compared to each monotherapy as measured by reduction of peak glucose concentrations or reduction of glucose AUC. In addition, after multiple dosing of the SGLT2 inhibitor and the
15 insulin alone and in combination in the animal models described hereinbefore, the effect on glycemic control can be determined by measuring the HbA1c value in blood. The combinations according to this invention significantly reduce HbA1c compared to each monotherapy.

20 The possible dose reduction of one or both of the SGLT2 inhibitor and the insulin can be tested by the effect on glycemic control of lower doses of the combinations and monotherapies in the animal models described hereinbefore. The combinations according to this invention at the lower doses significantly improve glycemic control compared to placebo treatment whereas the monotherapies at lower doses do not.

25 A superior effect of the combination of a SGLT2 inhibitor and a insulin according to the present invention on beta-cell regeneration and neogenesis can be determined after multiple dosing in the animal models described hereinbefore by measuring the increase in pancreatic insulin content, or by measuring increased beta-cell mass by morphometric analysis after
30 immunohistochemical staining of pancreatic sections, or by measuring increased glucose-stimulated insulin secretion in isolated pancreatic islets.

Pharmacological Examples

The following examples show the beneficial effect on glycemic control of the combination according to the present invention.

5 Example 1a:

The following example shows the beneficial effect on glycemic control of the combination of a SGLT2 inhibitor (compound (I.9)) and an insulin (insulin glargine) as compared to the respective monotherapies. All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental
10 authorities. Two weeks before the study starts, the rats were pretreated with a single dose of 60 mg/kg i.p. of streptozotocin to induced experimental diabetes, resembling a type 1 diabetic condition. During the study blood glucose was followed over 4 h in male, 3-h fasted Sprague-Dawley rats (CrI:CD) with an age of 8-9 weeks at the start of the study. A pre-dose blood sample was obtained by tail bleed for randomization and blood glucose was measured
15 with a glucometer 30, 60, 90 min and 2, 3, 4 hours after administration of the insulin and/or the SGLT2 inhibitor. At time point 0 min, the animals (n = 4-6 per group) were injected either with insulin glargine or isotonic NaCl subcutaneously. Simultaneously all animals received oral administrations of either vehicle alone (0.5% aqueous hydroxyethylcellulose) or this vehicle containing the SGLT2 inhibitor. The data are presented as mean±S.E.M. Statistical
20 comparison was conducted by repeated measures two-way ANOVA (analysis of variance) followed by Bonferroni post tests for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 1a. The term "Cpd. A" denotes the SGLT2 inhibitor compound (I.9) at a dose of 10 mg/kg. Insulin glargine was administered at a dose of 1.5 IU/animal. The term "Cpd. A + Insulin glargine"
25 denotes the combination of the SGLT2 inhibitor compound (I.9) and insulin glargine at the same doses. P values versus control are indicated by asterisks and p values of the monotherapies versus the combination are indicated by crosses (one symbol, p < 0.05; two symbols, p < 0.01; three symbols, p < 0.001). Four hours after administration, the SGLT2 inhibitor had reduced blood glucose by 19% versus control, and insulin glargine by 27%.
30 Both treatments did not show statistically significant differences versus control. The combination significantly decreased blood glucose by 53% versus control. The decreased blood glucose in the combination group was significantly different from the SGLT2 inhibitor monotherapy.

Example 1b:

The following example shows the beneficial effect on glycemic control of the combination of a SGLT2 inhibitor (compound (I.9)) and an insulin (insulin glargine) as compared to the respective monotherapies. All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental authorities. Two weeks before the study starts, the rats were pretreated with a single dose of 60 mg/kg i.p. of streptozotocin to induced experimental diabetes, resembling a type 1 diabetic condition. During the study blood glucose was followed over 6 h in male, 3-h fasted Sprague-Dawley rats (CrI:CD) with an age of 8-9 weeks at the start of the study. A pre-dose blood sample was obtained by tail bleed for randomization and blood glucose was measured with a glucometer 30, 60, 90 min and 2, 3, 4, 5, 6 hours after administration of insulin and/or the SGLT2 inhibitor. At time point 0 min, the animals (n = 4-6 per group) were injected either with insulin glargine or isotonic NaCl subcutaneously. Simultaneously all animals received oral administrations of either vehicle alone (0.5% aqueous hydroxyethylcellulose) or this vehicle containing the SGLT2 inhibitor. The data are presented as mean $\pm$ S.E.M. Statistical comparison was conducted by repeated measures two-way ANOVA followed by Bonferroni post tests for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 1b. The term "Cpd. A" denotes the SGLT2 inhibitor compound (I.9) at a dose of 10 mg/kg. Insulin glargine was administered at a dose of 1.5 IU/animal. The term "Cpd. A + Insulin glargine" denotes the combination of the SGLT2 inhibitor compound (I.9) and insulin glargine at the same doses. P values versus control are indicated by asterisks and p values of the monotherapies versus the combination are indicated by crosses (one symbol, p < 0.05; two symbols, p < 0.01; three symbols, p < 0.001). Six hours after administration, the SGLT2 inhibitor had reduced blood glucose by 13% versus control, and insulin glargine by 22%. Both treatments did not show statistically significant differences versus control. The combination significantly decreased blood glucose by 49% versus control. The decreased blood glucose in the combination group was significantly different from the SGLT2 monotherapy.

Example 2a:

The following example shows the beneficial effect on glycemic control of the combination of a SGLT2 inhibitor (compound (I.9)) and a low dose of an insulin (insulin glargine) as compared to a high dose of an insulin (insulin glargine). All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental authorities. Two weeks before the study starts, the rats were pretreated with a single dose of 60 mg/kg i.p. of streptozotocin to induced experimental diabetes, resembling a type 1 diabetic condition. During the study blood glucose was followed over 4 h in male, 3-h fasted Sprague-Dawley rats (CrI:CD) with an age of 8-9 weeks at the start of the study. A pre-dose blood sample was obtained by tail bleed for randomization and blood glucose was measured with a glucometer 30, 60, 90 min and 2, 3, 4 h after administration of the insulin alone or together with the SGLT2 inhibitor. At time point 0 min, the animals (n = 4-6 per group) were injected either with insulin glargine or isotonic NaCl subcutaneously. Simultaneously all animals received oral administrations of either vehicle alone (0.5% aqueous hydroxyethyl-cellulose) or this vehicle containing the SGLT2 inhibitor. The data are presented as mean±S.E.M. Statistical comparison was conducted by repeated measures two-way ANOVA followed by Bonferroni post tests for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 2a. Insulin glargine was administered at a dose of 1.5 IU/animal (low-dose) or 6 IU/animal (high-dose). The term "Cpd. A + low-dose insulin glargine" denotes the combination of the SGLT2 inhibitor at a dose of 10 mg/kg and insulin glargine at a dose of 1.5 IU/animal. P values versus control are indicated by asterisks and p values of the low-dose insulin glargine versus the combination or the high-dose insuline glargine are indicated by crosses (one symbol, p < 0.05; two symbols, p < 0.01; three symbols, p < 0.001). Four hours after administration, the low-dose insuline glargine had reduced blood glucose by 27% versus control without showing statistically significant difference. The combination had decreased blood glucose by 53%, which was in the range of the high-dose insulin glargine with a decrease of 47%. Both treatments were significantly different from the control.

Example 2b:

The following example shows the beneficial effect on glycemic control of the combination of a SGLT2 inhibitor (compound (I.9)) and a low dose of an insulin (insulin glargine) as compared to a high dose of an insulin (insulin glargine). All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental authorities. Two weeks before the study starts, the rats were pretreated with a single dose of 60 mg/kg i.p. of streptozotocin to induced experimental diabetes, resembling a

type 1 diabetic condition. During the study blood glucose was followed over 6 h in male, 3-h fasted Sprague-Dawley rats (CrI:CD) with an age of 8-9 weeks at the start of the study. A pre-dose blood sample was obtained by tail bleed for randomization and blood glucose was measured with a glucometer 30, 60, 90 min and 2, 3, 4, 5, 6 h after administration of insulin alone or together with the SGLT2 inhibitor. At time point 0 min, the animals (n = 4-6 per group) were injected either with insulin glargine or isotonic NaCl subcutaneously. Simultaneously all animals received oral administrations of either vehicle alone (0.5% aqueous hydroxyethylcellulose) or this vehicle containing the SGLT2 inhibitor. The data are presented as mean±S.E.M. Statistical comparison was conducted by repeated measures two-way ANOVA followed by Bonferroni post tests for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 2b. Insulin glargine was administered at a dose of 1.5 IU/animal (low-dose) or 6 IU/animal (high-dose). The term "Cpd. A + low-dose insulin glargine" denotes the combination of the SGLT2 inhibitor at a dose of 10 mg/kg and insulin glargine at a dose of 1.5 IU/animal. P values versus control are indicated by asterisks and p values of the low-dose insulin glargine versus the combination or the high-dose insulin glargine are indicated by crosses (one symbol, p < 0.05; two symbols, p < 0.01; three symbols, p < 0.001). Six hours after administration, the low-dose insulin glargine had reduced blood glucose by 22% versus control without showing statistically significant difference. The combination had decreased blood glucose by 49%, which was in the range of the high-dose insulin glargine with a decrease of 44%. Both treatments were significantly different from the control. The decreased blood glucose in the combination group did not show a statistically significant difference versus the high-dose insulin glargine group.

Example 3:

The following example shows the beneficial effect on glycemic control of a SGLT2 inhibitor (compound (I.9)) sequentially added to an insulin (insulin glargine) as compared to the insulin alone. All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental authorities. Two weeks before the study starts, the rats were pretreated with a single dose of 60 mg/kg i.p. of streptozotocin to induced experimental diabetes, resembling a type 1 diabetic condition. During the study blood glucose was followed over 8 h in male, non-fasted Sprague-Dawley rats (CrI:CD) with an age of 8-9 weeks at the start of the study. A pre-dose blood sample was obtained by tail bleed and blood glucose was measured with a glucometer 30, 60, 90 min and 2, 3, 4, 5, 6, 8 h after administration of insulin. At time point 0 min, the animals were injected with insulin glargine (n=10) or isotonic NaCl subcutaneously (n=5). At time point 120 (minutes) the

insulin glargine-treated mice were randomized according to blood glucose and separated in 2 groups (n=5 per group). Animals received oral administrations of either vehicle alone (0.5% aqueous hydroxyethylcellulose) or this vehicle containing the SGLT2 inhibitor. The data are presented as mean±S.E.M. Statistical comparison was conducted by repeated measures two-way ANOVA followed by Bonferroni post tests for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 3. Insulin glargine was administered at a dose of 1.5 IU/animal. The term "Insuline glargine/ Cpd. A" denotes the combination of insulin glargine at a dose of 1.5 IU/animal and the SGLT2 inhibitor at a dose of 10 mg/kg. P values versus control are indicated by asterisks and p values of the vehicle-treated group versus the animals treated with the SGLT2 inhibitor are indicated by crosses (one symbol, p < 0.05; two symbols, p < 0.01; three symbols, p < 0.001). The blood glucose between 2 and 8 hours was significantly decreased by 50% when compared to the vehicle-treated mice.

Example 4:

The following example shows the beneficial effect on body fat portion of a SGLT2 inhibitor (compound (I.9)) in combination with an insulin (as an insulin-releasing implant) as compared to the insulin (as an insulin-releasing implant) alone. All experimental protocols concerning the use of laboratory animals were reviewed by a federal Ethics Committee and approved by governmental authorities. Two weeks before the study starts, Sprague-Dawley rats (CrI:CD) were pretreated with a single dose of 60 mg/kg i.p. of streptozotocin to induced experimental diabetes, resembling a type 1 diabetic condition. Twice a day animals received oral administrations of either vehicle alone (0.5% aqueous hydroxyethylcellulose) or this vehicle containing the SGLT2 inhibitor (10 mg/kg). In additional groups, 1 or 2 insulin-releasing sticks were implanted subcutaneously in the neck of the rats. The SGLT2 inhibitor was administered to animals without or with 1 insulin implant. On day 27, the body fat was measured using the NMR technique. The data are presented as mean±S.E.M. Statistical comparison was conducted by one-way ANOVA followed by Bonferroni post tests/unpaired t-test for group-wise comparisons. A p value < 0.05 was considered to show a statistically significant difference. The result is shown in Figure 4. The term "Cpd. A" denotes the SGLT2 inhibitor at a dose of 10 mg/kg. P values versus control are indicated by asterisks and p values of the animals receiving 1 implant versus the combination of 1 implant and the SGLT2 inhibitor (denoted as "Cpd. A + 1 Implant") are indicated by crosses (one symbol, p < 0.05; two symbols, p < 0.01; three symbols, p < 0.001). Insulin-releasing implants significantly increased body fat portion (1 implant: +83%; 2 implants: +72%) when compared to controls.

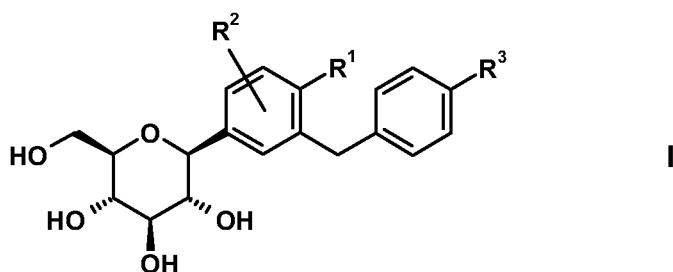
The combination of 1 implant and the SGLT2 inhibitor (denoted as "Cpd. A + 1 Implant") showed significantly lower body fat when compared to the rats receiving 1 implant alone.

Example 5:

- 5 Treating patients with type 1 diabetes with the pharmaceutical composition according to the invention, in addition to producing an acute improvement in the glucose metabolic situation, may contribute to a sustainable well metabolic situation in the long term. This may be observed in patients being treated for a longer period, e.g. 3 months to 1 year or even 1 to 6 years, with the pharmaceutical composition according to the invention and compared with
- 10 patients who are treated with insulin alone. There is evidence of therapeutic success compared with patients treated with insulin alone if no increase in the fasting glucose and/or HbA1c value is observed but where a reduction in hypoglycaemia event rate, glucose excursions or insulin requirement is seen. Further evidence of therapeutic success is obtained if a significantly smaller percentage of the patients treated with a pharmaceutical
- 15 composition according to the invention, compared with patients who are treated with optimized insulin alone, undergo a deterioration in the glucose metabolic position (e.g. an increase in the HbA1c value to >6.5% or >7%). For example a clinical study with 30 patients with type 1 diabetes (for example utilizing insulin pumps or receiving a therapy comprising a long-acting insulin) can explore the effect of the SGLT2 inhibitor (in particular the compound
- 20 (I.9), for example 10 or 25 mg once daily) as an adjunct to insulin with regards to safety and efficacy.

Patent Claims:

1. A pharmaceutical composition comprising
 (a) an SGLT2 inhibitor, and
 (b) an insulin.
2. The pharmaceutical composition according to the claim 1 wherein the SGLT2 inhibitor is selected from the group consisting of glucopyranosyl-substituted benzene derivatives of the formula (I)



wherein R^1 denotes Cl, methyl or cyano; R^2 denotes H, methyl, methoxy or hydroxy and R^3 denotes ethyl, cyclopropyl, ethynyl, ethoxy, (*R*)-tetrahydrofuran-3-yloxy or (*S*)-tetrahydrofuran-3-yloxy; or a prodrug thereof.

3. The pharmaceutical composition according to the claim 1 or 2 wherein the insulin is selected from the group consisting of:
 - rapid-acting insulins,
 - short-acting insulins,
 - intermediate-acting insulins,
 - long-acting insulins,
 including mixtures thereof.
4. The pharmaceutical composition according to the claim 1 or 2 wherein the insulin is a long-acting insulin.
5. The pharmaceutical composition according to one of the previous claims characterized in that the composition is suitable for combined or simultaneous or sequential use of the SGLT2 inhibitor and the insulin.

6. Method for treating a disease or condition selected from the group consisting of diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus and a disease or condition which requires treatment with insulin in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered in combination or alternation to the patient.
7. Method for treating a disease or condition selected from the group consisting of diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus and a disease or condition which requires treatment with insulin in a patient in need thereof characterized in that the patient receives a basal insulin therapy and in addition a SGLT2 inhibitor is administered to the patient.
8. Method for treating a disease or condition selected from the group consisting of
- for treating diabetes mellitus;
 - for treating diabetes mellitus, where treatment with insulin is required;
 - for treating type 1 diabetes mellitus;
 - for treating, preventing or reducing the risk of hypoglycemia;
 - for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;
 - preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, gestational diabetes, diabetes related to cystic fibrosis; or
 - improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
 - preventing, slowing, delaying or reversing progression from impaired glucose tolerance, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
 - preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis, myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; or

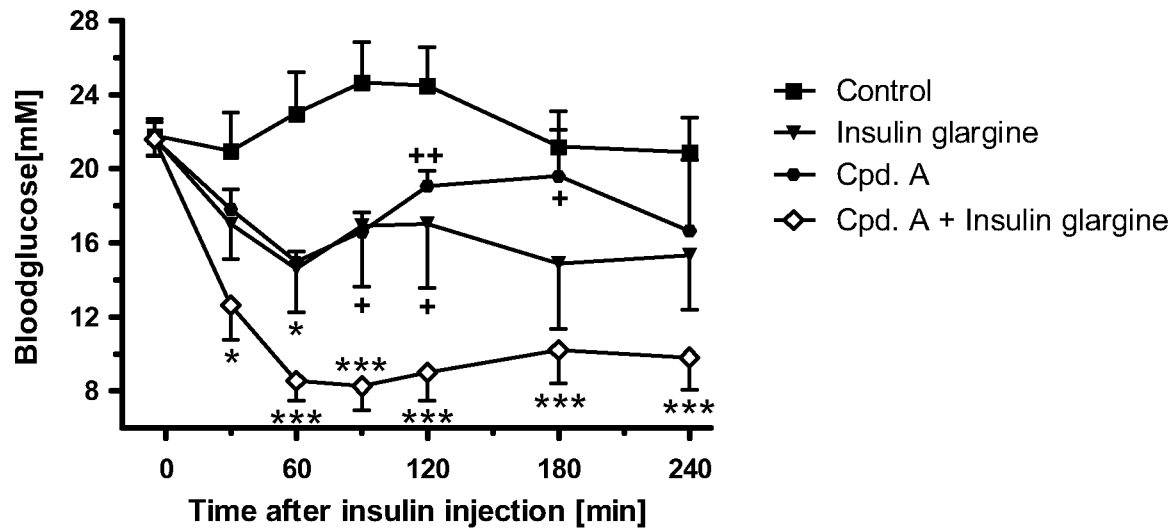
- reducing body weight and/or body fat or preventing or attenuating an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat; or
 - preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion; or
 - for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat; or
 - maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
 - preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
 - preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
 - treating hyperuricemia and hyperuricemia associated conditions;
 - treating or preventing kidney stones;
 - treating hyponatremia;
- in a patient in need thereof characterized in that an SGLT2 inhibitor and an insulin are administered in combination or alternation to the patient.
9. Use of a SGLT2 inhibitor according to claim 1 or 2 for the manufacture of a medicament for use in a method according to claim 6, 7 or 8.
 10. Use of an insulin according to claim 1, 3 or 4 for the manufacture of a medicament for use in a method according to claim 6, 7 or 8.
 11. Use of a pharmaceutical composition according to one of the claims 1 to 5 for the manufacture of a medicament for
 - for treating diabetes mellitus;
 - for treating diabetes mellitus, where treatment with insulin is required;
 - for treating type 1 diabetes mellitus;
 - for treating, preventing or reducing the risk of hypoglycemia;
 - for preventing, slowing progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus;

- 5
 - preventing, slowing the progression of, delaying or treating a metabolic disorder selected from the group consisting of type 1 diabetes mellitus, type 2 diabetes mellitus, impaired glucose tolerance, impaired fasting blood glucose, hyperglycemia, postprandial hyperglycemia, overweight, obesity, metabolic syndrome, gestational diabetes, diabetes related to cystic fibrosis; or
 - improving glycemic control and/or for reducing of fasting plasma glucose, of postprandial plasma glucose and/or of glycosylated hemoglobin HbA1c; or
 - preventing, slowing, delaying or reversing progression from impaired glucose tolerance, insulin resistance and/or from metabolic syndrome to type 2 diabetes mellitus; or
- 10
 - preventing, slowing the progression of, delaying or treating of a condition or disorder selected from the group consisting of complications of diabetes mellitus such as cataracts and micro- and macrovascular diseases, such as nephropathy, retinopathy, neuropathy, tissue ischaemia, diabetic foot, arteriosclerosis,
- 15
 - myocardial infarction, acute coronary syndrome, unstable angina pectoris, stable angina pectoris, stroke, peripheral arterial occlusive disease, cardiomyopathy, heart failure, heart rhythm disorders and vascular restenosis; or
 - reducing body weight and/or body fat or preventing or attenuating an increase in body weight and/or body fat or facilitating a reduction in body weight and/or body fat; or
- 20
 - preventing, slowing, delaying or treating the degeneration of pancreatic beta cells and/or the decline of the functionality of pancreatic beta cells and/or for improving and/or restoring the functionality of pancreatic beta cells and/or restoring the functionality of pancreatic insulin secretion; or
- 25
 - for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of ectopic fat; or
 - maintaining and/or improving the insulin sensitivity and/or for treating or preventing hyperinsulinemia and/or insulin resistance;
- 30
 - preventing, slowing progression of, delaying, or treating new onset diabetes after transplantation (NODAT) and/or post-transplant metabolic syndrome (PTMS);
 - preventing, delaying, or reducing NODAT and/or PTMS associated complications including micro- and macrovascular diseases and events, graft rejection, infection, and death;
 - treating hyperuricemia and hyperuricemia associated conditions;
- 35
 - treating or preventing kidney stones;
 - treating hyponatremia;

in a patient in need thereof.

12. Method according to one of the claims 6, 7 or 8 or use according to one of the claims 9, 10 or 11 wherein the patient is an individual diagnosed of one or more of the conditions selected from the group consisting of overweight, obesity, visceral obesity and abdominal obesity.

Figure 1a



5

Figure 1b

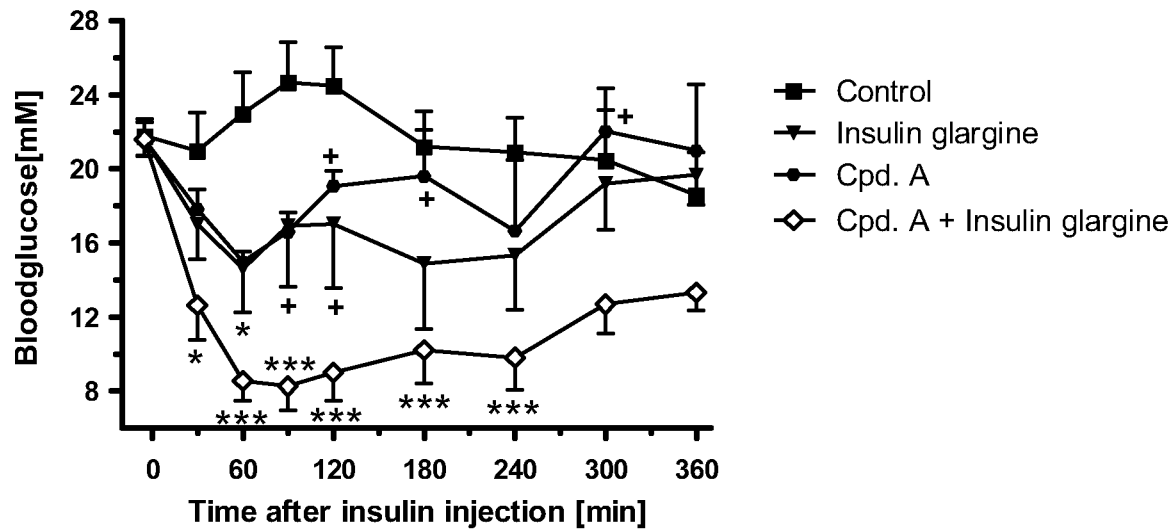


Figure 2a

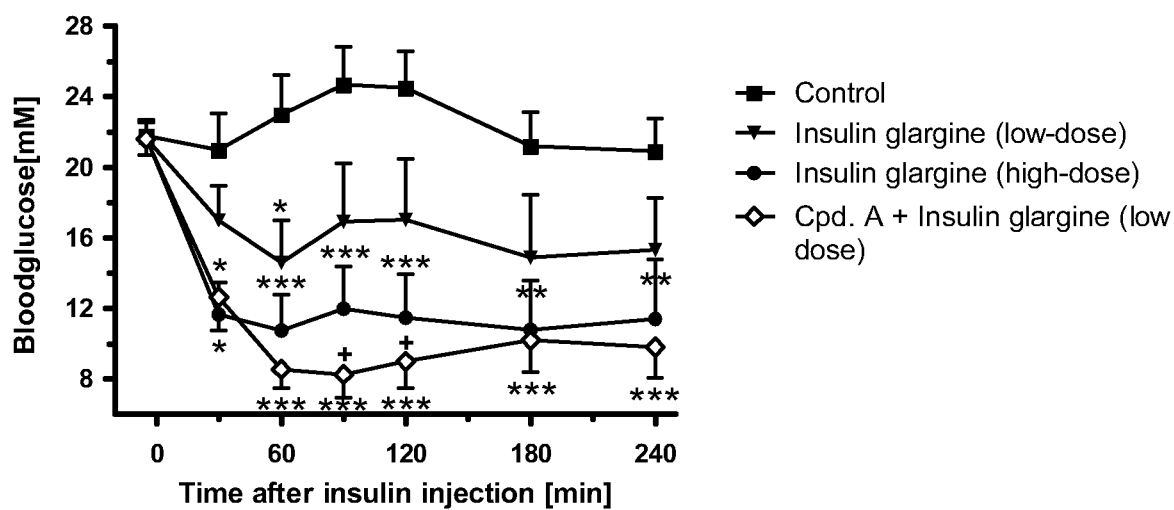


Figure 2b

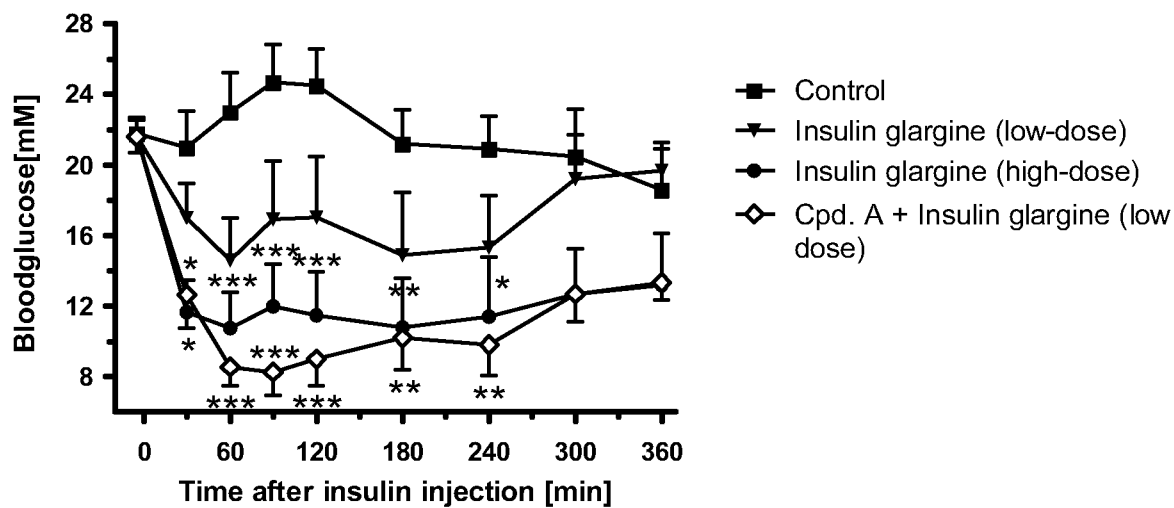


Figure 3

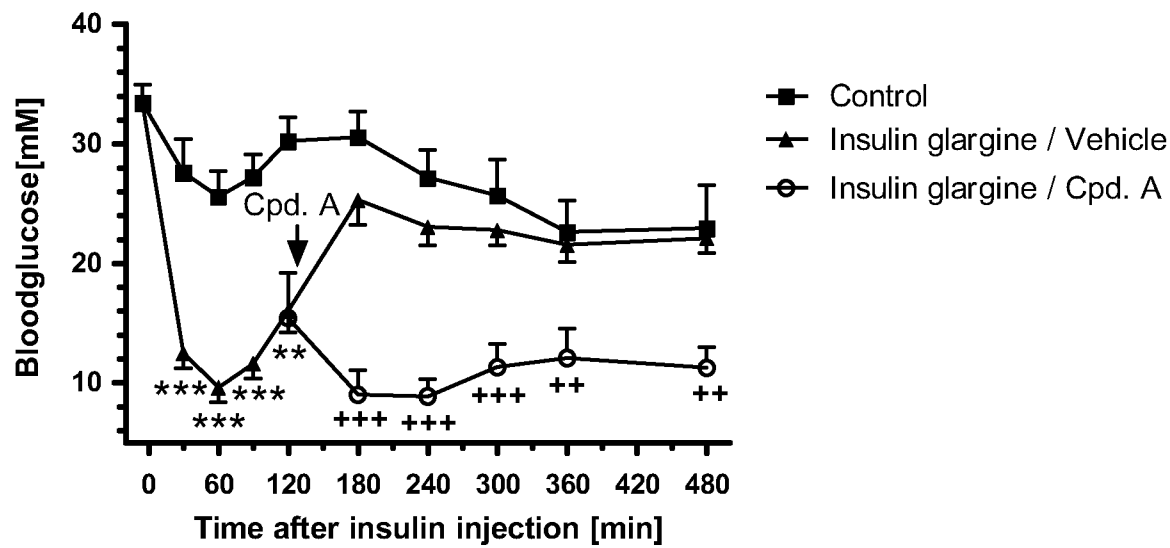
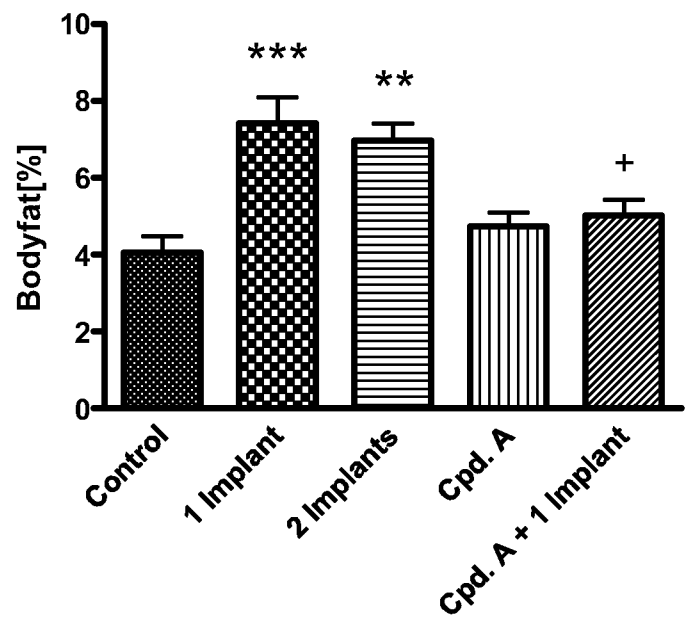


Figure4



INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/069532

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/00 A61K31/341 A61K38/28 A61P3/10
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 A61P

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/055940 A2 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; MANUC) 15 May 2008 (2008-05-15) cited in the application page 21 page 22, line 24 - line 30 page 28, line 15 - line 20 -----	1-12
X	WO 2008/116179 A1 (BRISTOL MYERS SQUIBB [US]; BINDRA DILBIR S [US]; DALI MANDAR V [US]; P) 25 September 2008 (2008-09-25) paragraph [0081] -----	1-12
X	WO 2006/034489 A2 (SQUIBB BRISTOL MYERS CO [US]; WASHBURN WILLIAM [US]; MENG WEI [US]) 30 March 2006 (2006-03-30) paragraph [0063]; claims 1,5 -----	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 document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"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

7 December 2011

Date of mailing of the international search report

15/12/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Loher, Florian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/069532

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008055940	A2	15-05-2008	AR 063627 A1 04-02-2009
		AU 2007316613 A1 15-05-2008	
		CA 2669043 A1 15-05-2008	
		CL 32272007 A1 04-07-2008	
		CN 101534815 A 16-09-2009	
		CO 6190509 A2 19-08-2010	
		EA 200900626 A1 30-12-2009	
		EP 2081569 A2 29-07-2009	
		JP 2010509283 A 25-03-2010	
		KR 20090089387 A 21-08-2009	
		MA 30875 B1 02-11-2009	
		TW 200826946 A 01-07-2008	
		US 2010298243 A1 25-11-2010	
		WO 2008055940 A2 15-05-2008	
		ZA 200902084 A 28-07-2010	
WO 2008116179	A1	25-09-2008	AR 065809 A1 01-07-2009
		AU 2008228714 A1 25-09-2008	
		CA 2681526 A1 25-09-2008	
		CN 101686988 A 31-03-2010	
		EA 200901277 A1 26-02-2010	
		EP 2139494 A1 06-01-2010	
		JP 2010522244 A 01-07-2010	
		KR 20090123964 A 02-12-2009	
		PE 01852009 A1 28-02-2009	
		TW 200904405 A 01-02-2009	
		US 2008234366 A1 25-09-2008	
		US 2011064801 A1 17-03-2011	
		WO 2008116179 A1 25-09-2008	
WO 2006034489	A2	30-03-2006	AR 051446 A1 17-01-2007
		AT 419260 T 15-01-2009	
		AU 2005286608 A1 30-03-2006	
		BR PI0516954 A 30-09-2008	
		CA 2581673 A1 30-03-2006	
		CN 101065391 A 31-10-2007	
		DK 1791852 T3 06-04-2009	
		EP 1791852 A2 06-06-2007	
		ES 2318570 T3 01-05-2009	
		HK 1098759 A1 09-04-2009	
		HR 20090113 T3 31-03-2009	
		JP 2008514625 A 08-05-2008	
		KR 20070054672 A 29-05-2007	
		NZ 553669 A 26-03-2010	
		PE 09692006 A1 24-09-2006	
		PT 1791852 E 20-03-2009	
		SI 1791852 T1 31-12-2009	
		WO 2006034489 A2 30-03-2006	
		ZA 200702158 A 27-08-2008	

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2011/069532

International filing date (day/month/year)
07.11.2011

Priority date (day/month/year)
08.11.2010

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/00 A61K31/341 A61K38/28 A61P3/10

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office

D-80298 Munich
Tel. +49 89 2399 - 0
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Loher, Florian

Telephone No. +49 89 2399-7839



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2011/069532

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
- ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:
- a. (means)
- ☐ on paper
 - ☐ in electronic form
- b. (time)
- ☐ in the international application as filed
 - ☐ together with the international application in electronic form
 - ☐ subsequently to this Authority for the purposes of search
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	
	No: Claims	<u>1-12</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-12</u>
Industrial applicability (IA)	Yes: Claims	<u>1-12</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1 WO 2008/055940 A2 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; MANUC) 15 May 2008 (2008-05-15) cited in the application
- D2 WO 2008/116179 A1 (BRISTOL MYERS SQUIBB [US]; BINDRA DILBIR S [US]; DALI MANDAR V [US]; P) 25 September 2008 (2008-09-25)
- D3 WO 2006/034489 A2 (SQUIBB BRISTOL MYERS CO [US]; WASHBURN WILLIAM [US]; MENG WEI [US]) 30 March 2006 (2006-03-30)

If not mentioned otherwise, the relevant passages are those mentioned in the International Search Report.

Claims 6-8 and 12 relate to a subject-matter considered by this Authority to be covered by the provision of Rule 39.1(iv)/67.1(iv) PCT.

The patentability can be dependent upon the formulation of the claims. The EPO, for example, does not recognise as patentable claims to the use of a compound in medical treatment, but may allow claims to a product, in particular substances or compositions for in a first or further medical treatment.

Art 33(2) PCT

The present application does not meet the requirements of Article 33(2) PCT, since the subject-matter of claims 1-12 is not new.

D1 discloses a composition comprising the present SGLT2 inhibitors and insulin for the treatment of diabetes and/or obesity. Therefore, the subject-matter of claims 1-12 is not new in the light of D1.

D2 discloses the combined use of dapagliflozin and insulin for the treatment of diabetes mellitus or obesity. Therefore, the subject-matter of claims 6-12 is not new in the light of D2.

D3 discloses a composition comprising one of the present SGLT2 inhibitors and insulin for the treatment of diabetes and/or obesity. Therefore, the subject-matter of claims 1-12 is not new in the light of D3.

Art 33(3) PCT

Examination of inventive step (Article 33(3) PCT) is not relevant for present claims 1-12 since the subject-matter of these claims is not new.

Art 33(4) PCT

The subject-matter of claims 1-12 is considered industrially applicable in the sense of Art 33(4) PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference P01 - 2679 / WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, item 5 below.	
International application No. PCT/EP2011/069532	International filing date (<i>day/month/year</i>) 07/11/2011	(Earliest) Priority Date (<i>day/month/year</i>) 08/11/2010
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6**bis**(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,

- ☒ the text is approved as submitted by the applicant
- ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

- ☒ the text is approved as submitted by the applicant
- ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

- a. the figure of the **drawings** to be published with the abstract is Figure No. 1
- ☒ as suggested by the applicant
- ☐ as selected by this Authority, because the applicant failed to suggest a figure
- ☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/069532

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/00 A61K31/341 A61K38/28 A61P3/10
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 A61P

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 practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/055940 A2 (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; MANUC) 15 May 2008 (2008-05-15) cited in the application page 21 page 22, line 24 - line 30 page 28, line 15 - line 20 -----	1-12
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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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

7 December 2011

Date of mailing of the international search report

15/12/2011

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Loher, Florian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/069532

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 2008055940	A2	15-05-2008	AR	063627 A1	04-02-2009
			AU	2007316613 A1	15-05-2008
			CA	2669043 A1	15-05-2008
			CL	32272007 A1	04-07-2008
			CN	101534815 A	16-09-2009
			CO	6190509 A2	19-08-2010
			EA	200900626 A1	30-12-2009
			EP	2081569 A2	29-07-2009
			JP	2010509283 A	25-03-2010
			KR	20090089387 A	21-08-2009
			MA	30875 B1	02-11-2009
			TW	200826946 A	01-07-2008
			US	2010298243 A1	25-11-2010
			WO	2008055940 A2	15-05-2008
			ZA	200902084 A	28-07-2010

WO 2008116179	A1	25-09-2008	AR	065809 A1	01-07-2009
			AU	2008228714 A1	25-09-2008
			CA	2681526 A1	25-09-2008
			CN	101686988 A	31-03-2010
			EA	200901277 A1	26-02-2010
			EP	2139494 A1	06-01-2010
			JP	2010522244 A	01-07-2010
			KR	20090123964 A	02-12-2009
			PE	01852009 A1	28-02-2009
			TW	200904405 A	01-02-2009
			US	2008234366 A1	25-09-2008
			US	2011064801 A1	17-03-2011
			WO	2008116179 A1	25-09-2008

WO 2006034489	A2	30-03-2006	AR	051446 A1	17-01-2007
			AT	419260 T	15-01-2009
			AU	2005286608 A1	30-03-2006
			BR	PI0516954 A	30-09-2008
			CA	2581673 A1	30-03-2006
			CN	101065391 A	31-10-2007
			DK	1791852 T3	06-04-2009
			EP	1791852 A2	06-06-2007
			ES	2318570 T3	01-05-2009
			HK	1098759 A1	09-04-2009
			HR	20090113 T3	31-03-2009
			JP	2008514625 A	08-05-2008
			KR	20070054672 A	29-05-2007
			NZ	553669 A	26-03-2010
			PE	09692006 A1	24-09-2006
			PT	1791852 E	20-03-2009
			SI	1791852 T1	31-12-2009
			WO	2006034489 A2	30-03-2006
			ZA	200702158 A	27-08-2008
