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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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P-2510

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. 10-036292

Solicitud de patente a nombre de **WORLD-TRADE IMPORT-EXPORT, WTIE, AG**

Yo, SILVANA MARIA LOPEZ DIAZ, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 No. 86-53, piso 6, obrando como apoderada de **WORLD-TRADE IMPORT-EXPORT, WTIE, AG**, domiciliada en Zug, Suiza, solicitante de la patente de la referencia, en respuesta al oficio No. 2556 notificado por fijación en lista el 19 de febrero de 2013, cuyo término fue prorrogado mediante escrito radicado el 2 de mayo de 2013, me permito manifestar:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial un nuevo capítulo reivindicatorio el cual comprende 1 a 4 reivindicaciones y reemplaza completamente el capítulo anterior.

En cuanto a estas modificaciones, me permito decir que las mismas no amplían de ninguna manera la materia objeto de la presente solicitud y se realizaron con el ánimo de superar las objeciones de claridad, planteadas por el examinador en su concepto técnico.

No se incluye un recibo de tasas porque el nuevo capítulo tiene menos reivindicaciones que el presentado originalmente.

2. Excepciones a la patentabilidad

En el punto número cuatro del examen técnico que se contesta, el examinador señala que el objeto de la reivindicación número 4 no es patentable de acuerdo al art. 20 D 486 (d) ya que se caracteriza por "*ser administrada*" aunque se encabece por la palabra composición.

Por tal motivo, se da respuesta positiva a dicho requerimiento, eliminando tal expresión de dicha reivindicación del capítulo reivindicatorio adjunto.

P-2510

3. Claridad de la solicitud

El examinador requiere excluir del título originalmente presentado la expresión “Y SU USO EN EL TRATAMIENTO DE LA OSTEOARTRITIS Y ENFERMEDADES RELACIONADAS”, con el fin de subsanar la objeción, se se ha eliminado dicha expresión para quedar de la siguiente manera: “COMPOSICION FARMACEUTICA COMPUESTA POR LA COMBINACION DE SULFATO DE CONDROITINA Y DIACEREINA”

El examinador objeta la claridad del capítulo reivindicatorio, argumentando que se debe excluir la siguiente expresión: *“para ser administrada por vía oral, la cual está indicada para el control y tratamiento de la osteoartritis y enfermedades relacionadas”*.

Con el fin de subsanar esta objeción, se ha redactado un nuevo capítulo reivindicatorio en el cual se ha excluido de la reivindicación 1 tal expresión.

4. Falta de Nivel Inventivo

El examinador objeta el nivel inventivo de la presente solicitud, argumentando que las anterioridades D1 y D2 ya sugerían las características de la reivindicación 1.

El examinador señala que el documento denominado D1 WO99/40926 A1 (NUTRAMAX LAB INC. US) y D2 es el estado de la técnica más cercano a la invención definida en la reivindicación 1, ya que manifiesta:

“D1 divulga una combinación con estos dos principios activos en concentraciones para Sulfato de Condroitina está en un rango desde 75 mg a 4g y para Diacereína 20 mg a 3g; administrado por vía oral, entre otras vías de administración utilizadas en donde los rangos de dosis en las composiciones varía dependiendo de las necesidades del humano o animal al cual se aplique (Págs. 21 a 24).”

El examinador considera que la diferencia entre la invención definida en la reivindicación 1 y los documentos citados son los rangos de concentración reivindicados para cada principio activo establecido en nuestra solicitud, pero que a pesar de dicha diferencia **“no se logra un efecto sorprendente”**, y que el problema técnico que pretende resolver esta invención se encuentra en *“¿cómo modificar la combinación de D1 como una alternativa con la misma actividad?”*.

Por lo anterior señala que, la solución que se provee no puede considerarse que envuelva un paso inventivo ya que *“la persona del oficio normalmente versada en la materia incluiría las concentraciones reveladas..... para llegar así al objeto de la reivindicación 1 de la solicitud”*.

Respetuosamente diferimos de la apreciación del Examinador. En primer término, en el documento D1 no se *divulga una combinación que comprenda los principios activos Sulfato de Condroitina + Diacereína como la reivindicada en nuestra invención*. Asimismo, en dicho documento no se aporta conocimiento técnico relacionado con nuestra invención por lo que **no puede considerarse divulgada la combinación** reivindicada, o bien que en base a este documento se pueda obviar o llegar fácilmente a nuestra invención.

Este documento al parecer, está describiendo un gran número de posibles combinaciones de compuestos, por lo que el problema técnico que resuelve dicho documento no está relacionado con nuestra invención, es decir, la provisión de un medicamento que comprende una combinación específica de dos activos: Sulfato de Condroitina y Diacereína en concentraciones específicas, con un efecto mejorado en comparación a cuando dichos principios activos son administrados en forma separada.

Como podemos apreciar, en este documento se describen las siguientes invenciones o grupos de invenciones:

Reivindicaciones 1, 2, 5 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende un aminosacárido, o un glicosaminoglicano (GAG) o uno o más fragmentos de un GAG y uno o más compuestos seleccionados del grupo consistente de L-ergotioneína, diacereína, ácido araquidónico y compuestos relacionados con tetraciclinas y el uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

Reivindicaciones 3, 4 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende S-adenosilmetionina (SAME) o pentosano y uno o más compuestos seleccionados del grupo consistente de superóxido dismutasa (SOD), L-ergotioneína, colágeno tipo II, diacereína, ácido araquidónico y compuestos relacionados con tetraciclinas y el uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

Reivindicaciones 6 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende superóxido dismutasa (SOD) y uno o más compuestos seleccionados del grupo consistente de L-ergotioneína, colágeno tipo II, diacereína, ácido araquidónico y compuestos relacionados con tetraciclinas y el

uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

Reivindicaciones 7 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende L-ergotioneína y uno o más compuestos seleccionados del grupo consistente de colágeno tipo II, diacereína, ácido araquidónico y compuestos relacionados con tetraciclinas y el uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

Reivindicaciones 8 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende colágeno tipo II y uno o más compuestos seleccionados del grupo consistente de diacereína, ácido araquidónico y compuestos relacionados con tetraciclina y el uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

Reivindicaciones 9 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende diacereína y uno o más compuestos seleccionados del grupo consistente de ácido araquidónico y compuestos relacionados con tetraciclina y el uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

Reivindicaciones 10 y 11:

Una composición para el tratamiento, reparación o prevención de daño al tejido conectivo que comprende ácido araquidónico y compuestos relacionados con tetraciclina y el uso de dicha composición para el tratamiento de humanos y animales en necesidad de este.

De lo anterior se desprende que un gran número de combinaciones posibles intentan ser reivindicadas en esta solicitud; sin embargo, no existe evidencia en la descripción que soporte la gran cantidad de compuestos mencionados. Por lo tanto, una persona normalmente versada en la materia no podría llevar a cabo lo descrito en dicha solicitud, ni tampoco podría deducir, por el simple hecho de haber mencionado en una tabla a los compuestos materia de nuestra solicitud, la sinergia resultante entre Condroitina y Diacereína actuado en una sola unidad de dosificación.

En este documento se mencionan diversas combinaciones de una gran cantidad de compuestos, entre los cuales se describe tanto al principio activo Condroitina como a la Diacereína, al activo L-ergotioneína, así como el Ácido Araquidónico y compuestos relacionados con Tetraciclinas, etc. Aunado a lo anterior, este documento fue redactado en términos muy vagos, poco claros, totalmente ambiguos para una persona del oficio normalmente versado en la materia.

Asimismo, en dicho texto se describe que se han investigado “*ciertas combinaciones*” de los agentes mencionados. También se menciona que “*ciertas combinaciones*” tuvieron efectos inhibitorios. No se especifica cuáles combinaciones han sido investigadas y que efectos tuvieron. Se declara que “*para varios estados patológicos estas novedosas interacciones estimuladoras e inhibitoras podrían ser benéficas. Por ejemplo, un estado hipermetabólico es parte de la patogénesis de algunas enfermedades*”.

De tal manera que a la luz de lo descrito en dicho documento, NO EXISTEN BASES para establecer que la combinación ha sido revelada o es parte del estado de la técnica, o bien considerar que con lo descrito en dicho documento una persona normalmente versada en la materia sería conducida a asociar un compuesto con otro esperando obtener un efecto inesperado o benéfico.

Por otro lado, el término usado en todo el cuerpo de la solicitud de patente D1 es “*tratamiento, reparación o prevención de daño a los tejidos conectivos*”, dicho termino es por demás ambiguo e incluye una gran variedad de enfermedades, síntomas, formas patógenas, desordenes, heridas etc., de las cuales una persona con conocimientos medios en la materia no tendría certeza para establecer cuál de todas las alteraciones posibles podría ser aplicable a todas las posibles combinaciones de las cuales se habla en esta solicitud.

En ningún momento se especifica que la combinación de Condroitina + Diacereína seria funcional, benéfica o aplicable para el tratamiento de la osteoartritis. Por lo tanto, no puede considerarse que exista indicio para establecer que una persona normalmente versada en la materia podría ser conducida en forma obvia a la combinación materia de la presente solicitud.

Por otra parte, el Examinador señala:

“...en la respuesta a las oposiciones se presenta un estudio realizado con una combinación de Sulfato de Condroitina (600mg) y Diacereína (50mg) por vía oral comparado con sólo Diacereína, lo cual no permite comprobar algún efecto sinérgico de la composición (combinación) que se reclama y los principios activos por separado; ya que la única forma de poder evaluar si existen o no ventajas en la combinación de compuestos (Sulfato de Condroitina 600mg y Diacereína 50mg), es a través de datos cuantitativos del efecto de cada uno de los compuestos por separado y de la combinación

de éstos, bajo las mismas condiciones de ensayo,...que sería inesperado, no predecible y que si tendría nivel inventivo; sobre todo cuando D1 ya mostraba la combinación de estos dos compuestos (composiciones Págs. 21-24).

Por lo anterior, en ausencia de un ensayo comparativo de la composición reivindicada con el arte previo, no es posible evidenciar un efecto técnico sinérgico..."

Sin embargo, como ya ha quedado anotado, el documento D1 no muestra ninguna combinación específica, mucho menos la relacionada con nuestra invención, y en lo relativo a la “ausencia de ensayo comparativo”, **dicha aseveración es incorrecta** debido a que en nuestra solicitud originalmente presentada consta el estudio clínico denominado:

“Estudio clínico de eficacia de la combinación Diacereína / Condroitina vs. Diacereína y Condroitina administradas de forma independiente”.

El Examinador ha omitido, en el examen técnico que se contesta, analizar los resultados arrojados por el estudio presentado en la Solicitud de Patente de la presente invención, en el cual se realiza un estudio comparativo de los datos cuantitativos del efecto de cada uno de los compuestos por separado y en combinación en las mismas condiciones de ensayo, mismo que debió **haber sido analizado y tomado en cuenta para la valoración de la actividad inventiva**.

En dicho estudio se demuestra claramente la superioridad de la combinación de Diacereína/Condroitina en comparación con Diacereína administrada individualmente y Condroitina administrada individualmente concretamente en el efecto modificador de la enfermedad (o en la estructura).

Tal y como se describió en la solicitud de patente, los fármacos para el tratamiento de la Osteoartritis están clasificados dentro de dos grupos: a) fármacos modificadores de síntomas, dirigidos a controlar el dolor, y b) fármacos modificadores de estructura, dirigidos a preservar el cartílago articular y frenar la evolución de la enfermedad.

Los primeros son los llamados SYSADOA (Symptomatic slow-acting drugs for the treatment of Osteoarthritis), llamados así ya que su inicio de acción es retardado en comparación con los activos antiinflamatorios no esteroideos, teniendo sus primeros efectos después de dos a tres semanas de terapia.

Los fármacos materia de nuestra invención, además de ser clasificados como aquellos denominados SYSADOA han sido investigados para determinar si también están clasificados como SMOAD (Structure-modifying osteoarthritis drugs).

El efecto modificador de la enfermedad (o en la estructura) de **CONDROITINA** ha sido objeto de análisis solo en pocos estudios llevados a cabo *in vitro* o *in vivo* en modelos animales de osteoartritis o degradación de articulaciones en las últimas décadas. En algunos de ellos se ha integrado esta valoración como primaria o bien secundaria.

Hasta antes de nuestra invención se llevaron a cabo alrededor de 6 estudios para valorar este efecto SMOAD de la **CONDROITINA**, tanto en rodilla como en las articulaciones de los dedos. **NO EXISTE NINGUN ESTUDIO QUE PRECEDA AL NUESTRO EN DONDE SE HAYA VALORADO EL EFECTO SMOAD DE LA CONDROITINA EN CADERA.**

Basados en los resultados de los estudios publicados se había concluido que la administración continua de **CONDROITINA** puede limitar o incluso parar la progresión radiológica de ambos: rodilla osteoartrosis femoro-tibial y dedo osteoartrosis interfalangeal; **sin embargo, este efecto solo se presenta en el tiempo MINIMO DE 1 AÑO A 3 AÑOS de administración continua.**

Se adjunta al presente en referencia de lo anterior, el **Anexo 2** denominado: "Chondroitin Sulfate as a structure□Modifying Agent". Daniel Uebelhart*, Ruud Knols*, Eling D de Bruin*, Gust Verbruggen. Department of Rheumatology and Institute of Physical Medicine, University Hospital, Zurich, Switzerland. Department of Biochemistry, Rush Presbyterian□St. Luke's Medical Center, Chicago, Illinois. Institute for Human Movement Sciences, ETH Zurich, Switzerland. Department of Rheumatology, Ghent University Hospital, Gent, Belgium. En dicho documento se analiza al activo Condroitina con la perspectiva de su efecto modificador y en el cual se señala expresamente lo siguiente (página 475 última parte y 476 primer párrafo):

"Chapter Overview.

...Based upon the results of these trials, it may be concluded that the daily oral administration of 800–1200 mg of chondroitin 4□ and 6□sulfate appears to be able to limit or even stop the radiological progression of both femoro□tibial knee OA and interphalangeal finger OA in a time frame of a minimum of 1 year to up to 3 years of continuous or intermittent administration of the compound."

"Resumen del capítulo.

...Basados en los resultados de estos estudios, podría concluirse que la administración oral de 800-1200 mg de condroitina 4 y 6 sulfato parece ser capaz de limitar o incluso detener la progresión radiológica de ambos, tanto OA femoro-tibial y OA dedo interfalángica, en un tiempo mínimo de 1 año hasta 3 años de administración continua o intermitente del compuesto.

(Traducción propia)”

En el caso de **DIACEREINA**, fueron identificados dos estudios de largo plazo, uno evaluando cadera y otro evaluando al activo en OA de rodilla, analizando la progresión estructural con mediciones radiográficas del espacio articular.

En el estudio realizado en cadera con una duración de **3 tres años**, se mostró un efecto de desaceleración en la progresión de la enfermedad estadísticamente significativa, mientras que el realizado en rodilla con duración de 1 año, no demostró reducción.

Dichos estudios se adjuntan al presente para mayor referencia como **Anexo 3** Dougados M, Nguyen M, Berdab L, Mazzières B, Vignon E, Lequesne M. “Evaluation of Structure-Modifying Effects of Diacerein in Hip Osteoarthritis.” *Arthritis & Rheumatism* 2001;44(11):2539–2547 y **Anexo 4** Pham T, Henanff AL, Ravaud P, Dieppe P, et al. “Evaluation of symptomatic and structural efficacy of a new hyaluronic acid (HA) compound, (NRD101), when compared to diacerein and placebo in one-year randomized controlled study in symptomatic knee osteoarthritis.” *Annals of Rheumatic Diseases* 2004;63(12):161–7.

A diferencia del estado de la técnica en donde claramente se establece que a efecto de que Condroitina tenga un efecto modificador en la estructura del cartilago habrá que administrarlo **POR PERIODOS DE MÍNIMO UN AÑO**, mientras que la Diacereína aún y existiendo evidencia de que presenta dicho efecto SMOAD no se ha logrado determinar plenamente su aportación y en todo caso, **LOS EFECTOS APARECERÁN DESPUÉS DE PROLONGADOS TIEMPOS DE TERAPIA**.

En cambio, la presente invención logra reducir la sintomatología de los pacientes que sufren de OA, como son la inflamación y el dolor, **ADEMÁS MANIFIESTA UN EFECTO MODIFICADOR DE LA ESTRUCTURA ARTICULAR**, frenando la evolución de la enfermedad y reduciendo el riesgo de que se manifiesten efectos secundarios, ya que actúa en corto plazo en comparación a cuando los activos actúan por separado. Es en dicho resultado donde se puede acreditar fehacientemente la sinergia de la combinación, ya que no es necesario esperar periodos prolongados de terapia para alcanzar los resultados esperados ya que tenemos que con la combinación se logra frenar la pérdida del espacio articular característico de la Osteoartritis en solo 6 meses de terapia.

En el estudio descrito en nuestra solicitud originalmente presentada se pueden apreciar los siguientes resultados:

“ESTUDIO CLINICO DE EFICACIA DE LA COMBINACION DIACEREINA / CONDROITINA VS. DIACEREINA Y CONDROITINA ADMINISTRADAS DE FORMA INDEPENDIENTE.

Se realizó un estudio clínico comparativo en pacientes con OA de cadera con duración de 6 meses de seguimiento. El estudio comparó la eficacia de la administración de Diacereína sola, Condroitina sola y la combinación de Diacereína/Condroitina. El estudio incluyó a 120 pacientes los cuales fueron divididos en 3 grupos de tratamiento:

Grupo 1: Diacereína 50 mg. dos veces al día.

Grupo 2: Condroitina 600 mg. dos veces al día.

Grupo 3: Diacereína 50 mg./Condroitina 600 mg. dos veces al día.

Se realizaron análisis de laboratorio al inicio del estudio y a los 6 meses de tratamiento, evaluándose el funcionamiento hepático y renal.

RESULTADOS.

Las características basales fueron comparables en los 3 grupos de tratamiento.

Grupo 1: Cuarenta pacientes.

Grupo 2: Cuarenta pacientes.

Grupo 3: Cuarenta pacientes.

Después de dos meses de tratamiento, 6 pacientes del Grupo 1 (Diacereína) suspendieron el tratamiento (por ineficacia). Ocho pacientes del Grupo 2 (Condroitina) suspendieron el tratamiento (por ineficacia). Ningún paciente del Grupo 3 suspendió el tratamiento durante los 6 meses de seguimiento.

Tabla 1. Características Basales.

Características	Grupos de Tratamiento		
	Grupo 1 (n= 34)	Grupo 2 (n= 32)	Grupo 3 (n= 40)
Edad promedio $\pm$ DS (años)	62.1 $\pm$ 7.0	63.0 $\pm$ 6.7	61.2 $\pm$ 6.0
Sexo masculino (%)	34	32	40
Índice de Masa Corporal (IMC) promedio $\pm$ DS (Kg./m ²)	25.4 $\pm$ 2.3	26.1 $\pm$ 3.0	26.0 $\pm$ 3.5
Duración enf. promedio $\pm$ DS.	4.8 $\pm$ 4.7	4.6 $\pm$ 4.3	5.1 $\pm$ 5.6
Localización de OA en los pacientes (%):			
Superolateral	48	54	56
Superomedial	24	26	25
Concéntrico	08	10	12
Ningún espacio articular	20	10	7
Severidad de los síntomas (EVA) promedio $\pm$ DS (mm.)	46 $\pm$ 18	45 $\pm$ 20	43 $\pm$ 22

El porcentaje de pacientes con progresión radiográfica se definió como la pérdida del espacio articular de al menos 0.5 mm, que fue significativamente más bajo en los pacientes del Grupo 3 que en los pacientes de los Grupos 1 y 2.

Los datos del primer análisis de laboratorio: 51.6% vs. 61.3% vs. **60.2%** [P= 0.035]. Los datos al terminar los 6 meses de tratamiento: 46.7% vs. 61.2% vs. **43.6%** [P= 0.006]. En relación a los objetivos que se cumplieron a los 6 meses de tratamiento con respecto al promedio del espacio articular fueron:

Grupo 1: Promedio $\pm$ DS 0.17 ± 0.24 mm/6 meses.

Grupo 2: Promedio $\pm$ DS 0.22 ± 0.22 mm/6 meses.

Grupo 3: Promedio $\pm$ DS 0.14 ± 0.20 mm/6 meses.

CONCLUSIONES.

El efecto modificador es la **mejora** reflejada en anchura del espacio articular, manifestada en el aumento de la capacidad global de la movilidad de la articulación, estabilización de la anchura del espacio articular, modulación del metabolismo de huesos y articulaciones.

El estudio con duración de 6 meses **mostró un efecto modificador de la estructura en la OA** de cadera en todos los grupos de tratamiento; sin embargo, **el tratamiento con la combinación Diacereína/Condroitina fue superior a los otros dos grupos.**

Todos los medicamentos fueron bien tolerados; sin embargo, la suspensión del tratamiento en algunos pacientes de los Grupos 1 y 2 fue debida a la lentitud de los efectos sobre la sintomatología de los pacientes.

Con lo antes descrito, claramente se evidencia **el efecto técnico sinérgico superior comparado con el mostrado cuando se utilizan individualmente** los compuestos Sulfato de Condroitina y Diacereína resultando que la combinación de ambos activos produce un EFECTO TERAPÉUTICO con MAYOR RAPIDEZ y MAYOR EFECTO MODIFICADOR en comparación al originado por la Diacereína y Condroitina prescritas separadamente y durante periodos prolongados de tiempo.

Por lo tanto, la invención manifiesta su superioridad, o ventaja **en la velocidad** con que se obtiene el efecto modificador del espacio articular.

Asimismo, el Examinador señala que el documento denominado D2, "Fármacos

de acción lenta para el tratamiento de la osteoartritis” con fecha de publicación del 25 de Octubre del 2006, describe las dosis conocidas de ambos activos así como los efectos secundarios en el tratamiento de la OA.

Efectivamente, el documento D2 es un artículo descriptivo de los fármacos de acción lenta recomendados para el tratamiento de la osteoartritis, entre los cuales se menciona el Sulfato de Glucosamina, Condroitin Sulfato, Diacereína, Acido Hialurónico y otros fármacos, describiéndose los resultados de algunos estudios relacionados con estos compuestos.

El Examinador nos indica en el oficio que nos ocupa lo siguiente:

“D2 menciona los principios activos Sulfato de Condroitina en dosis de 800mg a 1200mg (pág. 489) y Diacereína en las dosis de 50mg (mitad de dosis) y 100mg (dosis plena) (pág.490),....

En consecuencia, la persona del oficio normalmente versada en la materia, incluiría las concentraciones reveladas en el documento D2 en la combinación de D1 para llegar así al objeto de la reivindicación 1 de la solicitud. Por lo cual se considera obvia. “

Sin embargo debemos notar que en dicha publicación (D2) jamás se sugiere algún tipo de combinación mucho menos la combinación materia de nuestra invención, además, como se puede apreciar en las páginas 487, 489 y 490 se describen a cada uno de los fármacos materia de nuestra invención en forma **INDIVIDUAL**, por lo que no existen bases para asegurar que para una persona del oficio normalmente versada en la materia con lo descrito en dicho documento D2 resultaría obvia nuestra combinación así como el efecto sinérgico de la misma.

Aunado a lo anterior, es de notar lo que expresamente se señala en las conclusiones de dicho documento:

*“...en los diferentes estudios se obtiene una mejoría de los síntomas de la OA pero queda en entredicho el efecto condroprotector o modulador de estructuras como el cartilago. En los estudios realizados a largo plazo, de 2 ó 3 años de duración (26, 41, 60), los resultados obtenidos acerca de la sintomatología y de los cambios estructurales de las articulaciones **no se correlacionan**. Así los pacientes que disminuían la intensidad del dolor, no lo hacían en la progresión de la OA y viceversa.*

Como conclusiones decir que por el momento no hay un fármaco que haya demostrado modificar la enfermedad artrósica. La relación existente entre los cambios estructurales y el dolor, la funcionalidad o la evolución de la enfermedad, no se conoce todavía. La glucosamina, condroitin sulfato, diacereína y ácido hialurónico actúan sobre los

síntomas de la OA con un comienzo de acción lento, han demostrado una mejoría moderada en la sintomatología de la OA."

Por lo tanto, es claro que la aportación de dicho documento es de hecho contraria a lo aportado por nuestra invención, por lo que **no existen bases** para considerar que tanto el D1 o el documento D2 solos o en combinación afectan el nivel inventivo de nuestra solicitud.

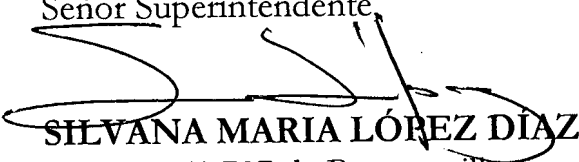
Finalmente, y a efecto de robustecer la evidencia de la aportación que hace al estado de la técnica nuestra invención, se ha realizado un cuadro y dos gráficas comparativas del Estudio clínico de la eficacia de la combinación Diacereína/Condroitina (100 mg/1200 mg por día) vs. Diacereína (100 mg/día) y Condroitina (1200 mg/día), administrados individualmente, donde se midieron los cambios estructurales en el cartílago en pacientes con OA de cadera, los cuales se adjuntan al presente como **Anexos 5, 6 y 7**.

En el Anexo número 5 consta un cuadro con los datos cuantitativos del estudio, mientras que en los Anexos 6 y 7 se graficaron los resultados de la Combinación vs. Condroitina y de la Combinación vs. Diacereína, respectivamente.

Con dichas graficas es palpable y evidente la mejora que presenta la combinación en comparación a la administración de los fármacos en forma independiente, con lo cual consideramos acreditado el nivel inventivo de nuestra invención.

En resumen, me permito decir que gracias a las modificaciones expuestas en el punto 1 de este memorial y los argumentos anteriormente mencionados, la presente solicitud cumple cabalmente con los requisitos de claridad y nivel inventivo respecto a la composición expuesta en el capítulo reivindicatorio adjunto. Por lo tanto, solicito comedidamente a ese despacho se sirva reconocer estos requisitos y conceder el privilegio de patente de invención a la solicitud en estudio.

Señor Superintendente,


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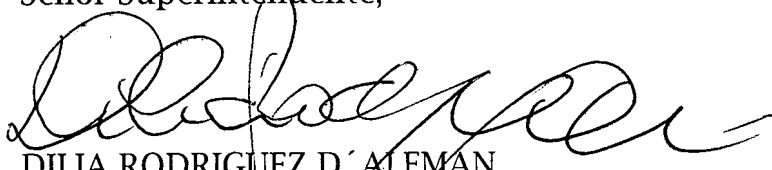
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

E. S. D.

REF: EXPEDIENTE No. 10.036.292
Solicitud de Patente a nombre de **WORLD-TRADE IMPORT-EXPORT,**
WTIE, AG.

Yo, **DILIA RODRÍGUEZ D' ALEMAN**, identificada como aparece al pie de mi firma, domiciliada en la Carrera 11 No. 86-53 Piso 6, Edificio Segovia Bogotá, Colombia, atentamente informo a usted que sustituyo el poder con que obro a la doctora **SILVANA MARÍA LÓPEZ DÍAZ**, domiciliada en Bogotá, identificada con la Cédula de Ciudadanía No. 22.468.787 y portadora de la tarjeta profesional No. 147.463 del CSJ, con las mismas facultades con que me fueron conferidas para este caso.

Señor Superintendente,



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Acepto sustitución

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PRESENTACION PERSONAL

El anterior escrito fue presentado ante el
NOTARIO ONCE DEL CIRCULO DE BOGOTA, D.C.
personalmente por Mr. Rodriguez

quien exhibió la c.c. 41.694.883 Bogotá

y Tarjeta Profesional No. 20274 C.S.J.

Fecha

18 JUN 2013

Guillermo Chávez Cristancho

NOTARIO



NOVEDAD DE LA INVENCION

Habiendo descrito la presente invención, se considera como novedad y, por lo tanto, se reclama como propiedad lo contenido en las siguientes

REIVINDICACIONES

1. Composición farmacéutica caracterizada porque esta compuesta por la combinación sinérgica de Sulfato de Condroitina y Diacereína, además de excipientes farmacéuticamente aceptables; en donde los principios activos se encuentran presentes en la formulación en un rango de concentración desde 600.0 mg. hasta 1.2 g. para el Sulfato de Condroitina y desde 50.0 mg. hasta 100.0 mg. para la Diacereína, mismos que se encuentran formulados en una sola unidad de dosificación oral.

2. Composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque el Sulfato de Condroitina se encuentra presente en la formulación en una cantidad de 600.0 mg. por unidad de dosis.

3. Composición farmacéutica de conformidad con la reivindicación 1, caracterizada porque la Diacereína se encuentra presente en la formulación en una cantidad de 50.0 mg. por unidad de dosis.

2/

4. Composición farmacéutica de conformidad con las reivindicaciones 1 a 3, caracterizada porque esta formulada en una sola unidad de dosificación oral en forma de cápsulas, tabletas o polvo en sobres.

14

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Chondroitin Sulfate as a Structure-Modifying Agent

I. Chapter Overview

The disease- or structure-modifying effects of chondroitin sulfate (CS) have been the focus of only a small number of studies performed *in vitro* or *in vivo* in animal models of osteoarthritis (OA) or joint degradation in the last decades. Some randomized controlled trials (RCTs) conducted on humans have integrated this feature as a primary or secondary evaluation outcome. The results of the survey conducted allowed the identification of a total of six RCTs performed in both knee OA and finger-joint OA. Only two groups, one in Belgium and one in Switzerland, have conducted these human studies. Based upon the results of these trials, it may be concluded that the daily oral administration of 800–1200 mg of chondroitin 4- and 6-sulfate appears to be able to limit or even stop the radiological progression of both femoro-tibial knee OA and interphalangeal finger OA in a time frame of a minimum of 1 year to up to 3 years of continuous or intermittent

administration of the compound. The fundamental basis of this structure-modifying effect must certainly be originating from the *in vitro* demonstrated capacity of CS to inhibit some of the key enzymes and cytokines involved in both the development and the progression of OA disease. This point should clearly be further investigated *in vivo* as well as possible other modes of action of CS on the joint structures as articular cartilage might not be the only target element involved in OA. Nevertheless, the results available so far of published RCTs do already provide a strong support for a disease-modifying effect of CS.

II. Introduction

The first attempts at improving structure and function of the connective tissues of synovial joints, thereby alleviating the symptoms of degenerative joint disorders, were based on the vague assumptions that an exogenous administration of precursors of extracellular matrix (ECM) components would help articular cartilage cells to replace the lost environment. This presumption prompted physicians to use substances such as glucosamine and sulfated glycosaminoglycans (GAGs), that is, CS aimed at improving cartilage repair in degenerative joint disease. Likewise, the first intra-articular administration of chondroitin polysulfate (CPS) was based on the presumption that this heparinoid type of drug would replace hyaluronan as a lubricant and reduces fibrinogen levels in inflamed joints and that this would bring some therapeutical advantage (Eylau, 1959, 1960). Unexpectedly, some patients reported symptomatic relief after having undergone this therapeutic procedure, and some changes in the biochemical composition of synovial fluid could also be assessed (Momburg *et al.*, 1976).

Together with a profound search in those mechanisms, whereby tissues are modified and/or destroyed during the course of inflammatory or degenerative joint diseases, researchers began to think about biological agents capable of restoring damaged connective tissues in a more methodical manner. As articular cartilage is one of the principal target tissue affected as a consequence of rheumatic disorders, many investigations focused on the metabolic characteristics of the single cell homing in this tissue: the chondrocyte. Substances that were demonstrated to protect articular cartilage during the course of destructive joint disorders were therefore termed "chondroprotective agents." When this occurred *in vivo* in joints affected by OA, these agents were designed as "disease modifying osteoarthritis drugs" (DMOAD) (Altman *et al.*, 2000).

As the auto/paracrine growth factor and cytokine cascades behind development, homeostasis, and destruction of the ECM of articular cartilage were not known previously, the first investigations on biological agents capable of modifying the structure of connective tissues in a positive way

concentrated mainly on the capability of these agents in improving the synthesis or impairing the degradation of ECM compounds, especially aggrecan and collagen. According to this definition, a number of substances could also be classified as connective tissue structure modifying agents (CTSMA). Among these, sulfated GAGs (chondroitin 4- and 6-sulfate and glucosamine), chemically modified tetracyclines, such as doxycycline and minocycline, and avocado/soybean unsaponifiables have been repeatedly cited.

A. Sulfated Polysaccharides and Chondroprotection

The so-called "chondromucoproteins" were among the first substances identified that were found to be able to improve the accumulation of ECM compounds (Kosher *et al.*, 1973; Nevo and Dorfman, 1972b; Nevo *et al.*, 1972a); they represent a mixture of proteoglycan (PG)-degradation products containing CS. It was then hypothesized that CS containing ECM-breakdown products somehow exerted a positive feedback on articular cartilage chondrocytes. The possibility of positively interfering with the *in vitro* connective tissue cell repair process using sulfated polysaccharides was first described in the mid 1970s (Schwartz and Dorfman, 1975; Verbruggen and Veys, 1977). A couple of years later, polysulfated CS was shown to improve the *in vivo* synthesis of hyaluronan in synovial joints of human subjects (Verbruggen and Veys, 1979). The same compound, as well as its naturally occurring analogue CS, was demonstrated to improve chondrocyte repair function *in vivo* in different experimental models of OA (Brennan *et al.*, 1987; Carreno *et al.*, 1986; Kalbhen, 1983; Uebelhart *et al.*, 1998a).

In addition, oral CS was also identified as a symptomatic slow-acting drug for OA (SYSADOA) as it was demonstrated in a couple of randomized, double-blind, placebo (PBO) controlled therapeutic trials (RCTs) that it was effective, with delayed onset of action, in alleviating the painful symptoms of OA (knee, finger, hip) and in improving the mobility of the OA joints as well as the overall mobility of the patient (see the corresponding chapter in this volume). For many years, CS was mostly documented as a SYSADOA but in some RCTs, with symptomatic efficacy as primary outcome, did also integrate the radiological progression as a secondary outcome. The quantitative radiological data provided by these studies supported further investigations regarding the structure-modifying effect of CS.

Therefore, RCTs provided results supporting that these CTSMA had DMOAD properties, as they were shown to retard the progression of human erosive OA in interphalangeal finger joints (Verbruggen and Veys, 1998a; Verbruggen *et al.*, 2002) and in knee joint as well (Uebelhart *et al.*, 1998b, 2004).

The objective of the present survey was to make a critical synthesis of the published literature available on RCTs regarding the structure- or

disease-modifying effect of orally administered CS in patients suffering from OA. Based upon the literature available and taking into consideration that the *in vitro* studies and the *in vivo* animal trials were already mentioned earlier, only data originating from RCTs focusing on human OA disease and specifically addressing finger and knee OA are reported here; indeed, there are no data originating from structure-modifying RCTs available so far regarding other joints, for example, hip or spine.

III. Methods

A. Search Strategy

A computer-aided search was conducted (Dickersin *et al.*, 1994), integrating all publications between 1966 and 2005, and reported in MEDLINE (Ovid, PubMed, Gateway; 1966 to June 2005) and the Cochrane Database of Systematic Reviews (2005); the aim was to identify all studies that cover the topic of chondroprotective effects of CS in knee and/or finger OA. Additionally, we checked the citation lists to complete our selection.

The following generic search terms (according to the thesaurus of each individual database) were used: chondroitin, chondroitin sulfate or sulfate, finger OA, joint disease, knee OA, musculoskeletal diseases, OA, randomized or randomised, rheumatic diseases, and any combination of these search terms. Some restrictions were made regarding the language of the original publications; only papers in English, French, German, or Dutch language were included into the review process.

B. Inclusion Criteria and Data Collection

To be included in the review, all studies had to have examined the effects of CS on OA *in vivo* in human subjects. In addition, only randomized controlled trials (RCTs) were included in this review. Studies using at least one of the following types of outcome were included: joint space narrowing, minimum- and mean-joint space width, Kellgren- and Lawrence-radiological score, X-rays. Disagreement regarding inclusion of some of the studies was resolved by consensus between the coauthors. RCTs evaluating CS in combination with glucosamine or nonsteroidal anti-inflammatory drugs were excluded from the review process.

C. Data Abstraction

Two of the coauthors defined as reviewers (RK, EdB) independently assessed the predefined outcomes of the studies according to a standardized form. Variability presented for the outcome "chondroprotective effects of

CS" was reported. If necessary, means and measures of dispersion were approximated from the available data, tables, and figures directly from the published papers. A p value of 0.05 was used as the criterion for statistically significant results.

IV. Results

A. Study Characteristics

The literature search yielded a total of six reports, which met the basic eligibility criteria of being an RCT conducted *in vivo* with human subjects. All human studies included had in common that their primary or secondary outcome assessed the effect of oral CS as a drug able to modify the OA-disease activity and/or improve the structure of the OA joint (chondroprotection). A total of three RCTs included knee OA patients, whereas three RCTs included patients with finger joints OA.

B. Disease-Modifying Effects of CS on RCTs in Knee OA

A total of three RCTs were available including 462 knee OA patients. Of the three studies that evaluated the chondroprotective aspects of CS in human knee joint (as primary or secondary outcome), all of them were originating from Switzerland. One study was a one-center study (Michel *et al.*, 2005) whereas the two other studies (Uebelhart *et al.*, 1998b, 2004) were multicentric and included patients from various countries (France, Italy, Belgium) as well.

Two CS treatment modalities were used, which differed in their administration sequence; one study (Uebelhart *et al.*, 2004) reported an intermittent treatment schedule of 2 × 3 months daily oral CS 800 mg treatment during 1 year; the two other studies used a treatment schedule of oral CS 800 mg daily given continuously for a total of 12 (Uebelhart *et al.*, 1998b) vs. 24 (Michel *et al.*, 2005) consecutive months.

At this point, it is important to say that disease-modifying effect of oral CS was the primary outcome of only one single RCT of 24-month duration (Michel *et al.*, 2005); regarding the two other 12-month duration studies mentioned, the chondroprotective effect of oral CS was only part of the secondary outcomes as these studies were primarily designed to test the symptomatic efficacy of the drug.

Uebelhart *et al.* (1998b and 2004) described that the radiological progression after 12 months showed significant decreased joint space width in the PBO group ($p < 0.01$), meaning a narrowing of the joint space, whereas there was no change in the CS treated group. These results were provided in those two studies in which the radiological outcome was not the primary

target of the study; in addition, the number of knee OA patients whose X-rays could be fully analyzed was relatively small, and the design of the studies was not identical in that the administration of CS was continuous (800 mg daily) in the first study (Uebelhart *et al.*, 1998b) and in the second (Uebelhart *et al.*, 2004), the administration of CS was intermittent (800 mg/day for two periods of 3 months each). The total duration was the same in both studies (12 months). Nevertheless, these initial exciting results provided the justification for the most recent clinical trial, which is the very first RCT with intention-to-treat analysis to be performed with structure-modifying effect as a primary outcome (Michel *et al.*, 2005). Indeed, long-term treatment with continuous oral CS (800 mg daily) over 2 years did stop the radiographic progression of knee OA (Michel *et al.*, 2005). Those patients who received a PBO ($n = 150$) experienced a significant decrease in their mean-joint width ($p = 0.04$) and their minimum joint space width ($p = 0.05$), whereas in sharp contrast, there was no joint space narrowing in the CS-treated group ($n = 150$). Therefore, the authors proposed that the clinical relevance of these positive results should be evaluated in further studies (Michel *et al.*, 2005). A new international multicentric study aimed at confirming the chondroprotective effect of oral CS was already launched including significantly more patients and more careful selection of the patients upon entry on strict radiological criteria. The results are awaited in 2006. In addition, a large longitudinal multicenter trial is also ongoing in the USA under the supervision of the NIH in which some OA patients do receive CS alone or CS + glucosamine sulfate. The first results are available (Clegg *et al.*, 2006). As the measurement of the progression of knee OA is based upon the radiological assessment of joint space narrowing in each of these RCTs, it appears important to discuss this major issue.

C. How to Measure the Structure or Disease-Modifying Activity of a Drug?

Based upon the European Agency for the Evaluation of Medicinal Products (EMEA) guidelines to test antiosteoarthritic drugs (CPMP, 1998), the best way to assess the chondroprotective activity of a drug would be to use the invasive arthroscopic procedure (Listrat *et al.*, 1997), but for obvious ethical reasons, this diagnostic method is generally not well accepted and adopted for clinical trials. The EMEA guidelines did also approve the use of a noninvasive indirect method based upon the analysis of the actual joint space measured on high quality X-rays of the knee joint. A couple of groups have been working on various procedures to develop this quantitative radiological method because the qualitative evaluation of the progression of knee OA using the Kellgren and Lawrence scoring system (Kellgren and Lawrence, 1957) has been demonstrated not to be sensitive enough to

evaluate the changes occurring in the OA joint and therefore might not be applicable in clinical trials. Considering the different methods of quantitative analysis of the X-rays proposed so far, Buckland-Wright and team developed an analysis of the joint space width using high-resolution plain film and double contrast macroradiographic investigation (Buckland-Wright, 1994; Buckland-Wright *et al.*, 1995), whereas Vignon and coworkers developed a system based on the digitalization of high-quality X-rays of the knee joint followed by an automatic or semiautomatic measurement of the joint space width (Fig. 1) with the assistance of a specific computer analysis software (Piperno *et al.*, 1998; Vignon *et al.*, 1999). In addition, based on the availability of high-quality X-rays, initially of the hip, later of the knee, Lequesne developed a method of analysis using a direct assessment of the joint width, called chondrometry, using a caliper (Lequesne, 1995). This method, which is certainly less sophisticated than the other two, nevertheless provided excellent results to assess the joint space loss in various types of OA, for instance in the rapid destructive type.

Considering the three RCTs taken into consideration in this survey, the quantitative assessment of joint space loss was performed by the original method of Vignon *et al.* (1999). More precisely, the measurement of the femoro-tibial joint space width was performed on standard weight-bearing antero-posterior X-rays of the knee joint in extension upon entry and after 12 months in the study of Uebelhart *et al.* (1998b), whereas standard antero-posterior X-rays of the knees were performed in weight-bearing monopodal position upon entry and after 12 months of follow-up in the CS intermittent administration study of Uebelhart *et al.* (2004). The only study with disease-modifying effect as primary outcome used standing, posteroanterior, weight-bearing X-rays of both left and right knees flexed to $\cong 20^\circ$ with patients

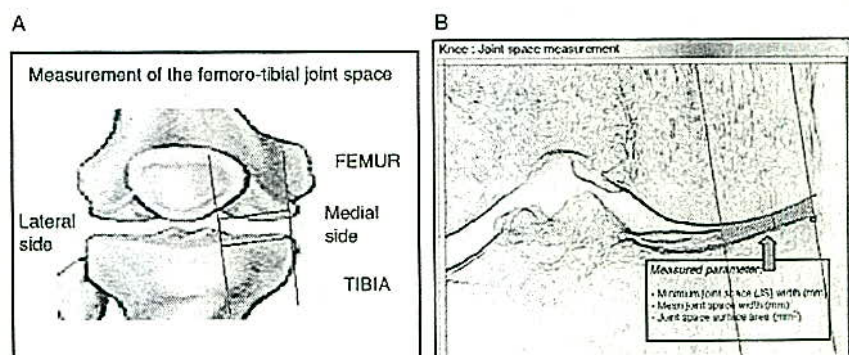


FIGURE 1 (A) Schematic view of the measurement of the femoro-tibial joint space. (B) After digitalization of the knee X-ray, definition of the zone of interest for automatic or semiautomatic measurement of the femoro-tibial joint space.

positioned with the toes up, directly under the edge of the cassette and the knees bent to lie against the cassette. The X-ray beam was directed 5° downward at a site midway between the popliteal spaces. A foot map was drawn for each patient in order to reproduce the position when radiographed after 24 months at the end of the study.

From these details, it can be shown that both the positioning of the patients for the radiographic procedure did change and improve from the initial to the latest studies and most importantly that the X-rays procedure itself evolved from a classical antero-posterior view to a posteroanterior view with the X-ray beam $\pm$ parallel to the tibial plateau with a semiflexed position. In order to increase the precision of the measurement of the joint space, one could further add the exact positioning of the knee joint (X-ray beam angulation) with fluoroscopy, a procedure initially developed by Vignon and now applied in some recent clinical trials, for instance in testing the effects of doxycycline on progression of OA (Brandt *et al.*, 2005). The evolution of these radiological procedures allowed to reach a greater degree of precision in the measurement of the femoro-tibial joint space narrowing in the longitudinal follow-up of OA disease and also to increase the reproducibility of the method, as it has been recently demonstrated that some important pitfalls can interfere with the accuracy of the measurement (Mazzuca *et al.*, 2004).

D. Disease-Modifying Effects of CS in Finger Joint OA

A total of two RCTs regarding finger OA patients as the target population could be identified including a total of 284 patients. The two studies referred in this survey were performed at the Department of Rheumatology, University of Ghent in Belgium.

The first study referred in two papers was published in 1998 (Verbruggen and Veys, 1998a; Verbruggen *et al.*, 1998b) and was based on the use of a numerical scoring system for the anatomical evolution of finger joint OA developed by Verbruggen and Veys (1996). A total of 119 patients suffering from finger OA were included in this RCT with the primary outcome being structure- and disease-modifying effect of oral CS4 and -6 given as 3×400 mg/day over a period of 3 years. Standard posteroanterior X-rays of the interphalangeal (IP) joints were carried out upon entry and at yearly intervals up to completion of the study after 3 years. It was shown that the progression of OA in the IP finger joints in an individual patient can be determined by the evolution of this joint in various previously described anatomical phases: not affected (N), classical OA (S), loss of joint space (J), erosive OA (E), remodeled joint (R). The structure-modifying effect of oral CS was assessed for by the number of patients developing OA in previously normal IP joints ($N > S$) or progressing through the described anatomical phases of the disease ($S > J$; $S > E$, $J > E$, $S > R$, $J > R$; $E > R$). The results of

24

this study showed that in the CS treated group of patients, there was a significant decrease in the number of patients with new erosive OA finger joints. The authors underlined this finding as being extremely relevant as it is known that finger OA becomes a clinical problem when pain and loss of function happen, which is when S joints progress to J and E joints. Indeed, during and after the E phase of anatomical progression, the finger joints will remodel and present with the nodular deformities characteristic of Heberden's and Bouchard's nodes.

Verbruggen *et al.* (2002) conducted two additional studies to assess the progression of finger OA and its modulation by two different DMOADs. Indeed, patients were included in two separate RCTs, but the results are reported and published in one single paper (Verbruggen *et al.*, 2002). A total of 45 patients received CPS (Arteparon®, Luitpold Werk, Munich, Germany), 50 mg intramuscularly twice weekly for 8 weeks every 4 months for a total duration of 3 years. A total of 34 patients received oral CS (Condrosulf®, IBSA, Lugano, Switzerland), 3 × 400 mg daily for a total duration of 3 years. Both the study with CPS and CS had a PBO group (total number of patients in the PBO group: $n = 85$). Standard posteroanterior X-rays of the IP finger joints were obtained at initiation of the trials and at yearly intervals up to completion of the studies after 3 years. Upon entry, almost 80% of the distal IP and 50% of the proximal IP joints were affected by OA. In a total of 40% of the patients, the classical picture of OA of the IP joints was complicated by manifest erosive OA changes. The two systems used to assess the progression of the anatomical lesions (Anatomical Lesion and Anatomical Phase Progression Score System) showed definite progression within 3 years, especially in the IP joints. When compared with the PBO controls, neither CPS nor CS was able to prevent the occurrence of OA in previously normal joints. However, when the classical OA associated anatomical lesions were considered, OA was less progressive in both CPS and CS groups. In addition, fewer patients treated with either CPS or CS developed erosive OA of the finger joints.

The authors conclude that the systems used to score the radiological progression of finger OA allowed to evaluate the structure-modifying effects of both DMOADs (CPS and CS), but they do also consider both studies as being pilot trials, which means that additional studies need to be performed in the future.

V. Discussion

Both *in vitro* and *in vivo* experiments made in various research centers regarding the effects on the metabolism of intercellular matrix molecules (collagens, PGs, aggrecan, hyaluronan) have shown that most (poly)-sulfated polysaccharides do influence connective tissue cells (chondrocytes,

73

synoviocytes, fibroblasts) in a similar way (Francis *et al.*, 1993; Verbruggen and Veys, 1977, 1992; Verbruggen *et al.*, 1999). With the improvement of our insights in the auto/paracrine growth factor and cytokine pathways that control the homeostasis of healthy connective tissues, it became possible to study the mechanism of action of these CTSMAs. Investigations with sulfated polysaccharides showed that these agents operate in biological systems through a down modulation of important catabolic auto/paracrine cytokine pathways, such as IL-1, thereby improving the accumulation of ECM compounds in the cell-associated matrix of these cells. Experiments conducted with bovine chondrocytes obtained from macroscopically intact metacarpophalangeal joints showed that physiological concentrations of CPS were able to significantly reduce the downstream IL-1 effects and reduce collagenase, proteoglycanase, MMP-1, and MMP-3 activities (Sadowski and Steinmeyer, 2002).

Furthermore, CPS inhibited the IL-1-induced mRNA expression of tPA (Sadowski and Steinmeyer, 2002). Likewise, xylosan polysulfate and CPS restored the accumulation of aggrecan, hyaluronan, and type II collagen in the cell-associated matrix in IL-1 β -treated human chondrocytes cultured in agarose. This effect probably resulted in part from the downregulation of the MMPs (Wang *et al.*, 2002). In cultured equine chondrocytes as well, CPS significantly reduced IL-1 β -enhanced expression of iNOS that was paralleled by an increased release of NO. CPS downsized nitrite concentrations in the supernatants of these IL-1 β -stimulated cultures (Tung *et al.*, 2002). Finally, a novel polysulfated polysaccharide cyclodextrin polysulfate showed cartilage structure-modifying effects *in vitro* as it improved the synthesis of aggrecan and the accumulation of cell-associated matrix macromolecules by human articular cartilage cells in alginate. Here, it was shown for the first time that this effect resulted in part from the direct repression of IL-1 as cyclodextrin polysulfate-treated cells expressed significantly lower amounts of intracellular IL-1 α and - β levels (Verdonk *et al.*, 2005). The same β -cyclodextrin-treated chondrocytes released significantly less IL-6 in the supernatant culture media, an effect being known to result from auto/paracrine IL-1 stimulation. It is important to remind at this point that the concentrations of the culture supernatant polysaccharide of most of the reported *in vitro* experiments are in the same order of magnitude than plasma or cartilage tissue polysaccharide levels obtained in humans after per oral administration (Muller *et al.*, 1983; Volpi, 2002, 2003).

These basic science considerations might explain why natural compounds registered as drugs, such as chondroitin 4- and 6-sulfate, might have, in addition to their symptomatic efficacy, some chondroprotective effects in OA disease as they are able to modulate key cytokines and enzymes directly involved in the development and the progression of the OA disease. Indeed, OA disease is a chronic joint disease characterized by flares and periods of increased inflammatory activity; these periods are responsible for

an increased degradation of matrix components and therefore the progression of the anatomical lesions.

As the results of our survey conducted to a small number of RCTs, which could be evaluated (total: $n = 6$), the present results should still be taken with some caution, and it seems important to wait for additional data regarding the structure-modifying effects of oral CS. In their meta-analysis of the structural and symptomatic efficacy of glucosamine and chondroitin in knee OA, Richy *et al.* (2003) reported positive results for glucosamine but no results for CS as of the time of this publication; there was no RCT available for CS with joint space narrowing as primary outcome.

In addition, an important question remains open, which is to know if drugs are always a suitable answer to disease modification in OA. As illustrated in a recent editorial of Dieppe (2005), there are still many unanswered questions regarding structural modification in OA, such as what is the clinical relevance of stopping the development of the OA process and if it really increases the quality of life of the patients, in addition to the difficult question of the price to pay to reach this goal.

VI. Conclusions

The results of this survey allowed the identification of a total of six RCTs in which some structure-modifying aspects have been evaluated as primary or secondary outcome. These studies focused on both knee OA and finger OA, but no data are available so far for other OA localizations such as hip and spine. On an evidence-based perspective, there are clearly not enough RCTs and data available so far to conclude that CS belongs to the category of the disease-modifying drugs for OA, but the available data in knee OA and finger OA provide a strong support to this hypothesis. Additional data from high-quality RCTs are awaited soon, which should allow an answer to this still open question.

Acknowledgments

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28

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25

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29

28

Evaluation of the Structure-Modifying Effects of Diacerein in Hip Osteoarthritis

ECHODIAH, a Three-Year, Placebo-Controlled Trial

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Objective. To evaluate the ability of diacerein, an interleukin-1 β inhibitor, to slow the progressive decrease in joint space width observed in patients with hip osteoarthritis (OA).

Methods. In this randomized, double-blind, placebo-controlled 3-year study, 507 patients with primary OA of the hip (by the American College of Rheumatology criteria) received diacerein (50 mg twice a day) or placebo. The minimal hip joint space width was measured by a central reader on yearly pelvic radiographs, using a 0.1-mm-graduated magnifying glass.

Results. Baseline characteristics were comparable in the 2 treatment groups (255 patients receiving diacerein, 252 receiving placebo); 238 patients (47%) discontinued the study, mainly because of adverse events in the diacerein group (25% versus 12% with placebo) and because of inefficacy in the placebo group (14% versus 7% with diacerein). The percentage of patients with radiographic progression, defined by a joint space loss of at least 0.5 mm, was significantly lower in patients receiving diacerein than in patients receiving placebo, both in the intent-to-treat analysis and in the completer analysis (50.7% versus 60.4% [$P = 0.036$] and 47.3%

versus 62.3% [$P = 0.007$], respectively). In those patients who completed 3 years of treatment, the rate of joint space narrowing was significantly lower with diacerein (mean $\pm$ SD 0.18 $\pm$ 0.25 mm/year versus 0.23 $\pm$ 0.23 mm/year with placebo; $P = 0.042$). Diacerein had no evident effect on the symptoms of OA in this study. However, a post hoc covariate analysis that took into account the use of analgesics and antiinflammatory drugs showed an effect of diacerein on the Lequesne functional index. Diacerein was well tolerated during the 3-year study. The most frequent adverse events were transient changes in bowel habits.

Conclusion. This study confirms previous clinical findings indicating that the demonstration of a structure-modifying effect in hip OA is feasible, and shows, for the first time, that treatment with diacerein for 3 years has a significant structure-modifying effect as compared with placebo, coupled with a good safety profile. The clinical relevance of these findings requires further investigation.

Osteoarthritis (OA) is the most prevalent and costly joint disease in older adults (1). In white adult populations ages 60 years and older, the prevalence of hip OA ranges from 17% in men to 9% in women (1,2). Hip OA is a major cause of morbidity, often resulting in a requirement for total hip replacement (THR) in 30–50% of patients after 10 years of the disease (3,4). Recent economic studies have evaluated the total cost per patient-year of OA in the US, with estimates ranging from \$543 to \$2,827, accounting for 5% of total insurance-plan expenses (5). The largest component of the total cost is hospital care (46%), mostly due to admission for THR (6).

Several approaches to the medical treatment of

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hip OA have been investigated, including nondrug and drug therapies (7). Of these medical treatments, nonsteroidal antiinflammatory drugs (NSAIDs) have been largely recommended by clinicians for the control of OA because they provide relief of mild-to-moderate symptoms; nevertheless, major gastrointestinal (GI) complications may occur with NSAIDs, especially in elderly patients (8). Moreover, the structural effect of such therapy in hip OA is not widely recognized; several observations have even suggested a deleterious effect on cartilage (9,10). Alternative medical therapies are currently being developed on the basis of a better understanding of the regulation of cartilage metabolism. Much of the attention is focused on identifying the agents responsible for the initial occurrence of matrix degradation. Current knowledge clearly indicates the involvement of matrix metalloproteases. Other data strongly support the evidence that cytokines, such as interleukin-1 β (IL-1 β) and perhaps tumor necrosis factor α , represent major catabolic systems that constitute the in situ source of the degradation of the articular tissue (11). In animal models, it has been shown that blocking IL-1 or its activity is very effective in the prevention of cartilage destruction (11).

Diacerein, a purified compound with anthraquinonic structure, has been shown to inhibit, in vitro (12) and in vivo (13), the production and activity of IL-1 and the secretion of metalloproteases (14), without affecting the synthesis of prostaglandins (15). In several animal models, diacerein has shown beneficial effects on cartilage by preventing or reducing the macroscopic and microscopic lesions of the joint tissue (16–18). Furthermore, in several clinical trials of 2–6 months' duration, diacerein significantly reduced, as compared with placebo, the pain and functional impairment in patients with hip or knee OA (19–21).

In order to investigate the potential structure-modifying effect of diacerein in OA, we carried out a 3-year, randomized, double-blind, placebo-controlled, multicenter clinical trial in patients with hip OA.

PATIENTS AND METHODS

Patients. Outpatients fulfilling the American College of Rheumatology criteria for the diagnosis of hip OA (22) were recruited for the study via 26 rheumatology departments in France. The clinical criteria for inclusion were the presence of symptomatic disease, as defined by the presence of daily hip pain for at least 1 month during the past 2 months and a Lequesne algofunctional index of at least 3 points (23). The radiographic criterion for inclusion was a joint space width (JSW) between 1 mm and 3 mm. If the JSW exceeded 3 mm,

it had to be at least 0.5 mm thinner than the JSW of the contralateral hip, measured at its narrowest point. The radiographic evidence of hip OA, the radiographic eligibility criteria, and the quality of the radiographic films were verified by a central reader (MN) before inclusion of a patient in the study.

The main criteria for exclusion were evidence of secondary hip OA (possibly due to injury, inflammatory or metabolic rheumatic disease, osteonecrosis, Paget's disease of bone, or hemophilia), medial femoral head migration, intraarticular injection or arthroscopy or corrective surgery of the hip joint during the 3 months prior to inclusion in the study, and total replacement of the contralateral hip joint <6 months prior to inclusion.

Study design. This prospective, multicenter, randomized, double-blind, 3-year, placebo-controlled study was conducted in accordance with the Declaration of Helsinki (1964) and its revision (1975), and was approved by the Institutional Review Board of the Cochin Hospital (Paris, France). Patients entered the study after reading and signing an informed consent form.

Drug administration and compliance. The patients were randomly assigned to receive one undistinguishable capsule of either placebo or diacerein at a dosage of 50 mg twice daily. The centralized allocation schedule was prepared using a blocked randomization technique (blocking factor of 4). Compliance with the study treatment was evaluated at each clinic visit by counting the number of capsules and empty treatment boxes returned by the patient, as well as by direct patient interviewing.

The patients were allowed to take analgesics and/or NSAIDs as rescue medication. However, before each clinic visit, they were required to undergo a 3-day and/or a 7-day washout period, respectively. Any systemic or intraarticular corticosteroid as well as other potential symptom-modifying drugs for OA were not allowed during the study. All treatments were recorded in the case report form at each clinic visit, throughout the study.

Evaluation of efficacy. Structural outcome measure. The structure of the OA hip was evaluated by radiography once a year and, according to the study protocol, at the time of withdrawal from the study. Pelvic radiographs were obtained with patients placed in a weight-bearing position and standing at 1 meter from the x-ray source, with a 20° internal foot rotation (24).

At the end of the study, each pelvic film was divided in 2 parts to permit the separate evaluation of each hip (the hip being evaluated, or "signal" hip, and the contralateral hip). All the films corresponding to either hip (signal or contralateral) of a patient were placed side-by-side on a light-box. The joint space was measured by one observer (the central reading expert radiologist [ML]) who was unaware of the patient's identity, study drug, signal hip, and sequence of the radiographs. The central reader determined the location of the narrowest point of the JSW (minimal JSW) on the radiographs of a given hip, then transferred this point to the other films of the set being measured. In cases in which no evidence of localized narrowing of the joint space could be detected on any film of the set, the upper point of the acetabular roof was evaluated. The anatomic limits for the measurement of the JSW were the bone contour of the femoral head and that of the acetabular roof, both of which were marked with a short stroke

of a dedicated pencil. Finally, the distance between these limits was measured using a 0.1-mm-graduated magnifying glass. The intraobserver reproducibility of this technique was considered to be acceptable (intraclass coefficient of correlation 0.963) (25). The measurement of the joint space was performed on all available radiographs; measurements obtained from radiographs taken right before a patient underwent surgery for THR were considered as "end-of-study data" and were analyzed in the same way as those obtained throughout the study.

Symptomatic outcome measures. At each 3-month-interval clinic visit, the functional impairment was evaluated by using the Lequesne index, which assesses a patient's function based on his or her responses to a questionnaire on daily activities during the previous week, with scores ranging from 0 to 24 (23). Pain in the joint was measured using a 100-mm visual analog scale, which assessed the pain occurring after physical activities during the previous week.

The consumption of the allowed rescue therapy (i.e., analgesics, NSAIDs) was evaluated by calculating the percentage of days between 2 clinic visits requiring such therapy. Moreover, the requirement for total replacement of the signal hip joint was recorded.

Evaluation of safety. At each clinic visit, the investigators evaluated the safety parameters. In addition, at the time of entry in the study and at month 6, as well as years 1, 2, and 3, blood samples were collected to evaluate biologic parameters as well as liver and kidney function. Finally, the overall assessment of the safety of the study treatment, by the investigator and by the patient, was recorded.

Statistical analysis. It was calculated that the inclusion of 250 patients per treatment group would be sufficient to demonstrate a difference in the progression of the joint space narrowing (JSN), with an α risk of 0.05 and a power of at least 0.90 (by 2-tailed testing). This calculation took into account an expected dropout rate of 10–15% per year.

In accordance with the International Conference on Harmonisation guidelines, the Scientific Committee of the Evaluation of the Chondromodulating Effect of Diacerein in OA of the Hip (ECHODIAH) study defined, in the study protocol, the primary populations to be analyzed: the intent-to-treat (ITT) population, which comprised all patients entering the study and having at least 1 pelvic radiograph obtained during treatment, and the completer population, comprising all patients receiving the study drug for a period of at least 34 months. Therefore, this analysis did not take into account the patients who withdrew from the study after baseline but did not undergo any further radiologic evaluation. For this reason, this analysis is referred to as the "modified" ITT analysis.

The primary efficacy end point of the study was the radiographic progression of OA, assessed by measuring the change in the minimal JSW of the signal hip. This end point was then expressed as the proportion of patients with radiographic worsening, defined by a decrease in joint space (i.e., JSN) of at least 0.5 mm during the study period. This threshold of 0.5 mm was determined from the results of a pilot study conducted in 30 patients; it corresponds to the lowest difference in JSW exceeding the measurement error and represents an actual radiographic progression (26,27). The progression was calculated in the 2 study groups by using the Kaplan-Meier technique, in which the event was defined by the first JSN of at

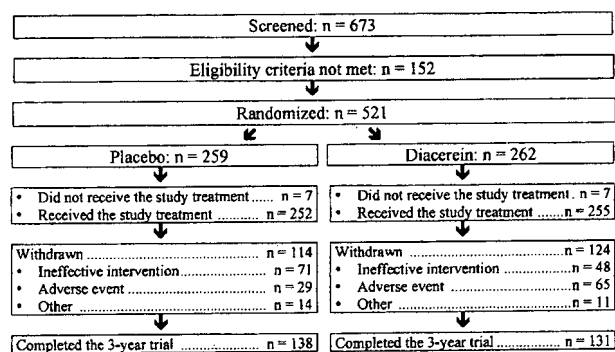


Figure 1. Screening of patients and study course in the Evaluation of the Chondromodulating Effect of Diacerein in Osteoarthritis of the Hip clinical trial.

least 0.5 mm observed during the study, as compared with the baseline JSW (28). The 2 survival curves obtained with this approach were then compared using the log rank test. The primary efficacy end point was also expressed as the magnitude of the narrowing of the joint, expressed as the JSN rate (in mm/year) between baseline and the end of the study. Due to the non-normal distribution of the radiographic variables, nonparametric tests were used and the results were expressed as the mean, SD, and median.

The changes in symptomatic outcome variables (pain and functional disability) in the treatment groups were compared by using analysis of variance, in both the ITT and the completer populations. The incidence of THR in the randomized population was evaluated using the Kaplan-Meier technique, in which the requirement for a surgical intervention for hip replacement defined the event. The analysis included the events occurring during the effective treatment period, plus a period of 3 months after treatment discontinuation. The 2 treatment groups were compared using the log rank test. Safety parameters were evaluated in all of the patients receiving the study treatment.

All analyses were performed using SAS (release 6.12; SAS Institute, Cary, NC) with PS/OS2. The level of significance was set at 0.05 by 2-tailed test for comparison with placebo.

RESULTS

Patients. Of 673 screened patients, 521 were considered eligible for the study and were randomized to receive treatment (Figure 1). The most frequent reason for noninclusion was either the lack of radiographic evidence of hip OA or an advanced disease with a JSW smaller than 1 mm at the narrowest point. Of these 521 patients, 14 who fulfilled the exclusion criteria did not receive any study treatment and were considered not qualified for the study. Therefore, a total of 507 patients received the study treatment. At the end of the 3 years, 124 of the 255 patients in the diacerein group (49%) and

Table 1. Withdrawals in the two treatment groups*

	Placebo (n = 252)	Diacerein (n = 255)
Total withdrawals	114 (45.2)	124 (48.6)
Reason for withdrawal		
Adverse events	29 (11.5)	65 (25.4)
THR	36 (14.3)	31 (12.2)
Inefficacy	35 (13.9)	17 (6.7)
Consent to withdrawal	10 (4.0)	10 (3.9)
Other	4 (1.6)	1 (0.4)

* Values are the number (%) of patients. THR = total hip replacement.

114 of the 252 patients in the placebo group (45%) had discontinued the treatment. The main reasons for discontinuation of the study treatment were adverse events in the diacerein group (25% as compared with 12% in the placebo group) and inefficacy in the placebo group (14% as compared with 7% in the diacerein group) (Table 1).

During the 3 years of the study, one radiographic evaluation under treatment was obtained for 446 patients (221 in the diacerein group and 225 in the placebo group); therefore, these patients formed the modified ITT population. A total of 269 patients (131 in the diacerein group and 138 in the placebo group) formed the completer population. A total replacement of the signal hip was performed in 87 patients (37 in the diacerein group and 50 in the placebo group; a preoperative radiograph was available for 31 and 44 of these patients, respectively).

The main baseline characteristics of the 507 patients are summarized in Table 2. The only difference between the 2 groups of patients concerned the localization of femoral head migration, which was more frequently located in the superolateral region of the hip in the diacerein group. A comparison of the baseline characteristics between completers and dropout patients (noncompleters) showed the presence of a more symptomatic and structurally severe OA at study entry in the noncompleter population ($P < 0.001$), as indicated by the levels of pain (41 ± 2 mm versus 49 ± 2 mm), the Lequesne functional index (7.2 ± 2.3 versus 8.5 ± 2.7), and JSW (2.4 ± 0.8 mm versus 2.1 ± 0.9 mm) in those who completed treatment compared with those who dropped out.

Compliance with the study treatment, evaluated by direct count, was satisfactory (i.e., >80%) in both treatment groups, but was slightly higher in the placebo group (94%, as compared with 91% in the diacerein group).

Efficacy. Radiographic criteria. The occurrence of radiographic progression (i.e., JSN) of at least 0.5 mm during the study was significantly lower and occurred later in the diacerein group as compared with the placebo group. This was observed in the modified ITT population (112 of 221 patients [50.7%] with diacerein versus 136 of 225 patients [60.4%] with placebo; $P = 0.036$ by log rank test), as well as in the completer population (62 of 131 patients [47.3%] with diacerein versus 86 of 138 patients [62.3%] with placebo; $P = 0.007$ by log rank test) (Figures 2 and 3). In the modified ITT population, this difference between the placebo group and the diacerein group was progressively larger during the study and reached statistical significance at the end of the third year. The cumulative rates in the patients with a radiographic progression of 0.5 mm were 29.2% with diacerein and 35.7% with placebo at the end of the first year, and 42.5% with diacerein and 50.2% with placebo at the end of the second year.

In the completer population, the mean values of the annual JSN rate were lower in the diacerein group (mean $\pm$ SD 0.18 ± 0.25 mm/year) as compared with the placebo group (0.23 ± 0.23 mm/year) ($P = 0.042$). The median values of the JSN rate during the study, as compared with baseline, suggest that the annual progres-

Table 2. Baseline characteristics of the 507 randomized and treated patients with hip osteoarthritis (OA), by treatment group

Characteristic	Treatment group	
	Placebo (n = 252)	Diacerein (n = 255)
Age, mean $\pm$ SD years	62.1 $\pm$ 7.0	63.0 $\pm$ 6.7
Sex, % male	41	39
Body mass index, mean $\pm$ SD kg/m ²	25.6 $\pm$ 3.5	26.0 $\pm$ 3.5
Disease duration, mean $\pm$ SD years	4.7 $\pm$ 4.6	5.0 $\pm$ 5.3
Hip OA localization, % patients		
Superolateral	48	53
Superomedial	24	19
Concentric	10	6
No joint space narrowing	18	22
Symptomatic severity		
Pain score on visual analog scale, mean $\pm$ SD mm	46 $\pm$ 19	44 $\pm$ 21
Functional impairment by Lequesne index, mean $\pm$ SD score	7.8 $\pm$ 2.5	7.9 $\pm$ 2.6
Patient's assessment on Likert scale, % patients		
None	2	2
Mild	22	21
Moderate	54	49
Severe	21	26
Very severe	1	2
Structural severity by joint space width, mean $\pm$ SD mm	2.25 $\pm$ 0.85	2.33 $\pm$ 0.85

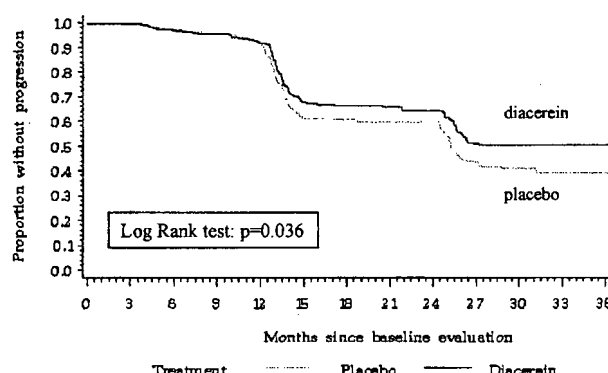


Figure 2. Proportion of patients in the intent-to-treat population with at least 2 radiographs without radiologic progression (i.e., a change in joint space width ≥ 0.5 mm) during the study. The 2 time-to-event curves (obtained according to the method of Kaplan and Meier) were compared using the log rank test.

sion was stable in the placebo group (0.19 mm/year, each year), whereas it progressively declined in the diacerein group (0.18 mm/year at the end of the first year, 0.14 mm/year at the end of the second year, and 0.13 mm/year at the end of the third year). The difference in the median values of annual JSN rates between the 2 groups during the third year of the study can be interpreted as a sparing effect of 32% obtained with the diacerein treatment, as compared with placebo. In the analysis of the ITT population, the mean ($\pm$ SD) values of the JSN rate were 0.39 ± 0.81 mm/year in the placebo group ($n = 225$) versus 0.39 ± 0.75 mm/year in the diacerein group ($n = 221$). The median values of the JSN rate were 0.23 mm/year in the placebo group versus 0.19 mm/year in the diacerein group. This difference did not reach statistical significance.

Symptomatic efficacy criteria. In terms of symptomatic outcome measures, the results showed a significant improvement from baseline in the clinical symptoms in both treatment groups. However, no statistically significant difference between groups was observed in the ITT or completer populations (Table 3). Similarly, no difference was observed in the consumption of analgesics and NSAIDs. Nevertheless, a post hoc exploratory analysis of covariance (using, as covariates, the baseline values of the measurements, the duration of treatment administration, and the consumption of analgesics and NSAIDs) showed the presence of beneficial effects on the Lequesne index ($P < 0.05$) and on the pain levels ($P = 0.063$) due to treatment with diacerein.

Requirement for total hip replacement. THR of the signal hip during the study and during the 3 months

following discontinuation of the study treatment was performed in 87 patients: 37 in the diacerein group (14.5%) and 50 in the placebo group (19.8%). The comparison of the survival curves of the 2 groups showed a trend in favor of the diacerein treatment that did not reach statistical significance ($P = 0.286$ by log rank test).

Safety. The number of patients experiencing any adverse event was significantly different between treatment groups: 95% in the diacerein group versus 84% in the placebo group ($P = 0.001$). Most of these events were mild-to-moderate in intensity. Table 4 summarizes the most commonly observed adverse events.

Diarrhea was the most frequent side effect (46% in the diacerein group versus 12% in the placebo group; $P = 0.001$). The severity of diarrhea was mild-to-moderate in both groups (76% with diacerein and 78% with placebo); nevertheless, diarrhea caused discontinuation of the treatment more frequently in the diacerein group (12% versus 2% in the placebo group). Diarrhea while on treatment with diacerein usually occurred within the first 2 weeks (mean delay 8.5 days). There was no difference between diacerein and placebo in terms of upper GI symptoms.

The most frequent urinary event with diacerein was a discoloration of urine, which was of no clinical significance. Several events in the skin and appendages system (pruritus, rash, eczema) occurred more frequently in the diacerein group. No clinically relevant differences were observed between the diacerein and placebo groups with regard to vital signs and laboratory analyses (blood and urine). The overall tolerability assessment during the study was rated as "good or

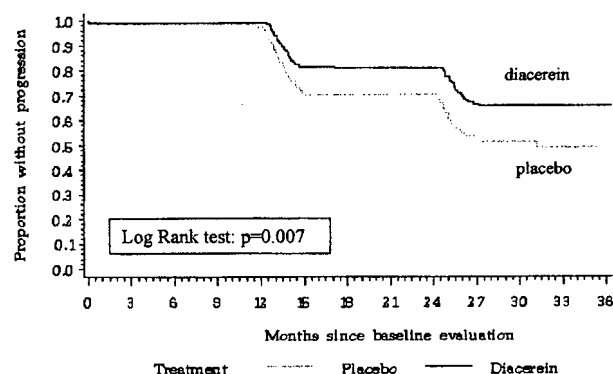


Figure 3. Proportion of patients in the completer population without radiologic progression (i.e., a change in minimal joint space width ≥ 0.5 mm) during the study. The 2 time-to-event curves (obtained according to the method of Kaplan and Meier) were compared using the log rank test.

Table 3. Changes from baseline in symptomatic outcome measures during the 3 years of treatment in patients with hip osteoarthritis receiving either placebo or diacerein (100 mg daily)

Parameter	Intent-to-treat analysis		Completer analysis	
	Placebo (n = 247)	Diacerein (n = 246)	Placebo (n = 138)	Diacerein (n = 131)
Pain (100-mm visual analog scale)				
Mean $\pm$ SD	-3.0 $\pm$ 29.9	-3.0 $\pm$ 30.2	-10.7 $\pm$ 29.1	-6.6 $\pm$ 30.1
Median	-2.0	-5.0	-14.0	-9.0
Function (Lequesne index)				
Mean $\pm$ SD	-0.5 $\pm$ 4.2	-0.5 $\pm$ 4.0	-1.5 $\pm$ 4.2	-1.2 $\pm$ 4.1
Median	-0.5	-1.0	-1.5	-1.5

excellent" by 81–93% of the patients in the diacerein group and by 95–99% in the placebo group.

DISCUSSION

This 3-year, placebo-controlled study expands our knowledge on the natural evolution of hip OA and shows that the long-term daily intake of diacerein slows the progression of JSN in hip OA.

Pain severity and the development of severe disability are important outcome measures in OA. However, it seems reasonable to use surrogates, such as radiographically assessable changes, to monitor disease progression in OA. There is good evidence that by favorably modifying the natural history of OA in terms of structural changes, long-term clinical benefit will occur in a large proportion of patients (29). For the evaluation of the potential structure-modifying effect of a drug, various scientific societies (29–31) recommend the use of change in minimal JSW as a radiographic variable for the assessment of progression. This parameter was the primary end point of the ECHODIAH study. In this study, the hip films were obtained using a

standardized procedure, with the patients in standing position. Other studies have been conducted evaluating the hip JSW by using supine radiography (32,33). However, recent clinical trials other than ECHODIAH have also been conducted using standing radiographs (34). Moreover, recent data suggest a lack of influence, or merely a weak influence, of the patient's positioning on the radiologic evaluation of hip JSW (25). Finally, the standing radiography method is the one recommended by the Task Force of the Osteoarthritis Research Society International (30).

The clinical relevance of radiographic progression is best expressed by presenting the results on an individual basis, that is, by calculating the percentage of patients with a relevant JSN progression during the study. There are no available data that propose a precise value for the change in minimal JSW that would define a structural change and reflect a "clinically relevant" progression. Therefore, we used a cutoff value that was defined from the results of previous studies and that excludes the measurement error due to the technique. This cutoff was based on the evaluation of reproducibility (as recommended by Bland and Altman [35]) and has also been previously referred to as the minimum individual difference (36) or as the smallest detectable difference (37). Based on the above evidence, the Scientific Committee of the ECHODIAH study concluded that a change in the minimal JSW of at least 0.5 mm, measured with this technique, would indeed represent a "relevant" structural progression.

In accordance with the recommendations of the World Health Organization and of the International League Against Rheumatism, the percentage of patients with a relevant progression was calculated by taking into account all of the pelvic radiographs available during the study and using the time-to-event analysis in which the event was defined by the occurrence of a joint space loss of at least 0.5 mm (28). This analysis demonstrated a

Table 4. Most commonly observed adverse events during the 3 years of the study in patients with hip osteoarthritis receiving either placebo or diacerein (100 mg daily)*

Adverse event	Treatment group		P†
	Placebo (n = 252)	Diacerein (n = 255)	
Skin and appendage disorders	16 (6)	31 (12)	0.024
Rash or pruritus	7 (3)	17 (7)	
Gastrointestinal disorders	115 (46)	185 (73)	0.001
Diarrhea	31 (12)	117 (46)	
Dyspepsia	17 (7)	11 (4)	
Urinary system disorders	31 (12)	104 (41)	0.001
Discoloration of urine	6 (2)	79 (31)	

* Values are the number (%) of patients.

† Statistical significance determined by the Mann-Whitney U test.

statistically significant difference in favor of treatment with diacerein as compared with placebo in the modified ITT as well as in the completer populations.

A statistically significant effect of the treatment was only observed in the completer population, when the analysis focused on the changes in JSW regressed in mm/year. Indeed, the comparison of the baseline characteristics of the patients who completed the 3 years of the trial (completers) with those of the dropouts (non-completers) showed that the patients who had to discontinue the study treatment had a more severe OA at study entry and a more rapid progression. In the modified ITT analysis, this baseline difference between completers and dropout patients may lead to an inaccurate calculation of the annual JSN rate of the dropouts. For example, for a patient who lost 0.4 mm of JSW (a reduction within the range of measurement error) during a 3-month period before withdrawal, an erroneous annual JSN rate of 1.2 mm/year would be attributed by using a "last observation carried forward" approach. On the other hand, the approach is justified for the patients who completed the 3-year study (completer population).

It has to be pointed out that the evidence of a difference in disease severity between the dropouts and completers should not be viewed as a potential bias for the interpretation of the primary results, since this difference was observed in both treatment groups, for patients who left the study for inefficacy, and in view of surgery for THR. Furthermore, a radiograph was obtained before withdrawal in the majority (75%) of the dropouts and the joint space of the dropouts was measured and analyzed in the same way as that of the patients who completed the study.

The dropout rate observed during ECHODIAH was within the expected range and is consistent with the rates observed in OA trials of similar duration, such as the "Link" study of tiaprofenic acid (10) with a dropout rate of 54% over 3 years, the 2-year study of diclofenac which had a dropout rate of 43% (38), and the study of naproxen and acetaminophen with a dropout rate of 65% over 2 years (39).

Another finding of ECHODIAH that needs to be addressed concerns the effects of the study treatment on the clinical symptoms. No significant differences were found between groups, although beneficial effects of diacerein on pain and functional impairment of OA have been previously established in several placebo-controlled trials (19–21). However, the results observed in ECHODIAH should not be regarded as surprising, due to the characteristics of the patients and the design of the trial. The patients in this 3-year structural trial had

lower baseline levels of pain and functional impairment than did those of patients included in previous short-term (12–24 weeks) studies evaluating the symptomatic effects of diacerein. Moreover, during the 3 years of ECHODIAH, symptomatic rescue treatments, such as analgesics and/or NSAIDs, were permitted and in 41% of the patients, the scheduled washout period for these drugs before the clinic visits was not rigorously observed. The persistence of the effects of these concomitant treatments may prevent the clear demonstration of a symptomatic effect of diacerein. However, the post hoc analysis of covariance that took into account these confounding factors revealed the presence of the beneficial effects of diacerein on symptoms.

The requirement for joint replacement can be considered as a potential outcome measure. The importance of this criterion for the evaluation of the clinical relevance of structure-modifying drugs for OA has been previously suggested (40). In the ECHODIAH study, the risk of a requirement for hip replacement surgery was 19.8% in the placebo group versus 14.5% in the diacerein group. This difference did not reach statistical significance. THR is not yet generally accepted as an outcome measure, due to the wide differences in local health strategies and clinical indications. Therefore, before any definite conclusion, further studies are necessary in order to evaluate both the clinical relevance of such outcome measures and the minimum intergroup difference that would be considered clinically relevant.

The results of ECHODIAH regarding the effectiveness of diacerein must be considered together with the safety profile of the product that was observed during this 3-year study. The reported adverse events were as expected, since they were not different from those observed during previous clinical trials with diacerein. The side effects were mostly related to changes in bowel habits resulting in diarrhea, abdominal pain, and soft stools (41). The discoloration of the urine was also an expected phenomenon during treatment, due to the urinary elimination of a metabolite of diacerein, and this was without clinical significance. In the end, this long-term study confirms the good safety profile of diacerein, on the upper GI tract in particular, that has been previously shown in several short-term clinical studies.

In conclusion, the ECHODIAH study permitted us to appreciate previously unknown aspects of the design of clinical trials for the investigation of structure-modifying treatments. Furthermore, the study showed that diacerein can slow the progressive decrease in joint space in patients with hip OA, with a good safety profile

over the long term. Future studies will improve the understanding of the clinical relevance of these results.

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33

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APPENDIX A: THE ECHODIAH INVESTIGATORS STUDY GROUP

In addition to the authors, the following investigators, all in France, also participated in the ECHODIAH study: Pierre Acquaviva (Marseille), Maurice Alcalay (Poitiers), Francis Blotman (Montpellier), Bernard Combe (Montpellier), Joël Dehais (Bordeaux), Bernard Delcambre (Lille), Liana Euler-Ziegler (Nice), Jean-Louis Kuntz (Strasbourg), Bruno Larget-Piet (Creteil), Xavier Le Loet (Rouen), Guy Llorca (Pierre-Benite), Gérard Loyau (Caen), Emmanuel Maheu (Paris), Christian Marcelli (Cannes), Charles-Joël Menkes (Paris), Jean-Baptiste Paolaggi (Boulogne-Billancourt), Yves Pawlotsky (Rennes), Xavier Phelip (Grenoble), Jacques Pourel (Vandoeuvre les Nancy), Jean-Luc Sebert (Amiens), Christian Tavernier (Dijon), Richard Treves (Limoges), and Jean-Pierre Valat (Tours).

37

EXTENDED REPORT

Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis

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Objective: To evaluate long term efficacy of three iterative courses of three weekly intra-articular (IA) injections of NRD101 in the treatment of symptomatic knee osteoarthritis (OA).

Patients and methods: A 1 year prospective, multicentre, randomised, double blind, placebo controlled study of 301 patients aged >50 years with painful and radiological medial knee OA. Patients were randomly assigned into three groups receiving: (1) three courses of three IA injections of hyaluronic acid (HA) + oral placebo; (2) IA injections of saline solution + diacerein 100 mg/day; (3) IA injections of saline solution + oral placebo. Demographic data and symptomatic criteria—pain, Lequesne's index, patient's global assessment of disease activity, percentage of painful days—were obtained during the study; primary structural criterion was JSW. Efficacy criteria were changes in pain VAS, joint space narrowing (JSN), and percentage of progressors (JSN >0.5 mm). An intention to treat analysis was used for symptomatic variables, and complete analysis for structural variables.

Results: Baseline characteristics were similar between the three groups. Mean (SD) improvement in pain VAS was clinically relevant (−33.9 (27.3), n=301), but with no difference between the groups (p=0.96). JSW deteriorated (−0.09 (0.55) mm, n=277, p=0.01), but with no difference between the groups (p=0.82). Percentages of progressors were 17.7, 18.9, and 20.3% (p=0.90), in groups 1, 2, and 3, respectively.

Conclusion: A weak but statistically significant structural deterioration occurred over 1 year, together with clinically relevant symptomatic improvement in patients receiving oral drug and iterative IA injections. Symptomatic and/or structural effects for both this new HA compound and diacerein were not demonstrated.

Osteoarthritis (OA) is a major cause of disability and is among the most prevalent form of musculoskeletal diseases.^{1 2} Drugs for the treatment of OA have been classified as symptom modifying and structure modifying drugs. Until now, no drug can be included in the latter category. However, several compounds could be considered as potentially delaying the disease progression.^{3–5} These potentially structure modifying drugs can be classified according to their administration route: by mouth—for example, diacerein or glucosamine sulphate, or intra-articular (IA)—for example, hyaluronic acid (HA).

Diacerein, a purified compound with an anthraquinone structure, has been shown to inhibit, in vitro and in vivo, the production and activity of interleukin 1 and the secretion of metalloproteinases, without affecting the synthesis of prostaglandins.^{6–9} There is evidence that diacerein has both a significant symptomatic (pain) and a structural effect compared with placebo, at least in hip OA.^{3 10 11}

HA is a high molecular weight polysaccharide, which is a major component of synovial fluid and cartilage. In OA, the molecular weight and concentration of HA are diminished. The concept of viscosupplementation suggests that IA injection of HA might help to restore the viscoelasticity of the synovial fluid.¹² HA has been used as a pain reliever for patients with OA, particularly in the knee joint.^{12–14} Furthermore, data have suggested that HA may have a

beneficial structural effect in OA.^{4 15} However, the efficacy of this treatment remains the subject of debate.^{16–18}

NRD101 is a new HA compound produced from *Streptococcus equus* by fermentation on vegetable or synthetic based mediums not containing human or animal based products. Its average molecular weight is 1.900 kDa (concentration 1%, 25 mg of sodium hyaluronate in 2.5 ml; Hoechst Marion Roussel). In phase II and III studies in Japan, various treatment schedules were studied using five or more infiltrations at various concentrations and volumes, from which they determined that NRD101 was safe and that the optimal dosage was 2.5 ml weekly (unpublished data). A preliminary open study compared the efficacy of five weekly courses of IA injections of NRD101 and another HA compound, Artz (0.600–1.200 kDa) in 182 patients with knee OA. Patients had to evaluate the treatment efficacy at the end of the study using a seven level Likert scale. In the NRD101 group (n=95), 72.6% of the patients considered their treatment at least moderately effective compared with 58.6% in the Artz group (n=87), p<0.05.^{19 20}

The main purpose of our study was to evaluate the long term symptomatic and structural efficacy and safety of three

Abbreviations: HA, hyaluronic acid; IA, intra-articular; JSN, joint space narrowing; JSW, joint space width; NSAIDs, non-steroidal anti-inflammatory drugs; OA, osteoarthritis; VAS, visual analogue scale

IA injection sequences of NRD101 over 1 year in the treatment of symptomatic knee OA, compared with diacerein and with placebo. As far as we know, this study is the first comparing a potential oral structure modifying drug with an IA anti-osteoarthritic drug in knee OA.

PATIENTS AND METHODS

Patients

Outpatients fulfilling the American College of Rheumatology clinical or radiological criteria for the diagnosis of knee OA were recruited for the study through 46 rheumatology departments in France.

The main inclusion criterion was the presence of a symptomatic primary painful medial femorotibial knee OA defined by a daily pain visual analogue scale (VAS) score >30 mm in the previous month. If both knees were symptomatic, only the most painful one was taken into account. The radiographic inclusion criterion was medial joint space width (JSW) >2 mm. The radiographic evidence of knee OA, eligibility criteria, and the quality of the radiographic films were verified by a central reader (PhR) before inclusion of a patient in the study.

The main exclusion criteria were evidence of secondary knee OA (possibly due to injury, inflammatory or metabolic rheumatic disease, osteonecrosis, Paget's disease, villonodular synovitis, haemophilia); prior intra-articular HA treatment; other IA injection, including lavage and corticosteroids within the previous 3 months; treatment with diacerein in the 3 months before inclusion and use of any other anti-osteoarthritic drugs in the 2 months before inclusion; contra-indication to IA injection (anticoagulants, haematological anomalies); and severe knee OA (JSW <2 mm, surgery required on the evaluated knee in the year).

Study design

This prospective, multicentre, randomised, double blind, 12 month, placebo controlled study was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent endorsements, and was approved by the review board of the Cochin Hospital, Paris, France. Patients entered the study after reading and signing an informed consent form.

Drug administration

The patients were randomly assigned to receive one undistinguishable capsule of either placebo or diacerein at a dose of 50 mg twice daily as well as three courses, every three months, of three weekly IA injections of either saline solution or HA (NRD101).

The randomised allocation schedule was centralised (Cassenne Laboratories, Osny, France). According to a pre-established randomisation code, the treatment sequence was: (a) 3x3 HA IA injections (NRD101) and daily placebo capsules; or (b) 3x3 IA injections of saline solution and daily diacerein capsules; or (c) 3x3 IA injections of saline solution and daily placebo capsules. The saline vehicle was expected to have only a placebo effect and was considered as an IA control. Whatever the treatment group, the IA injection procedure was the following: subcutaneous lidocaine local anaesthesia, aspiration of synovial fluid (if present), and injection of the 2.5 ml contained in the pre-filled syringes. The practitioner who carried out the injections did not evaluate the patient to avoid evaluation bias.

All treatments were recorded in the case report form at each clinic visit throughout the study. Patients were allowed to take analgesics as rescue drug. However, before each evaluation visit, they were required to undergo a 2 day

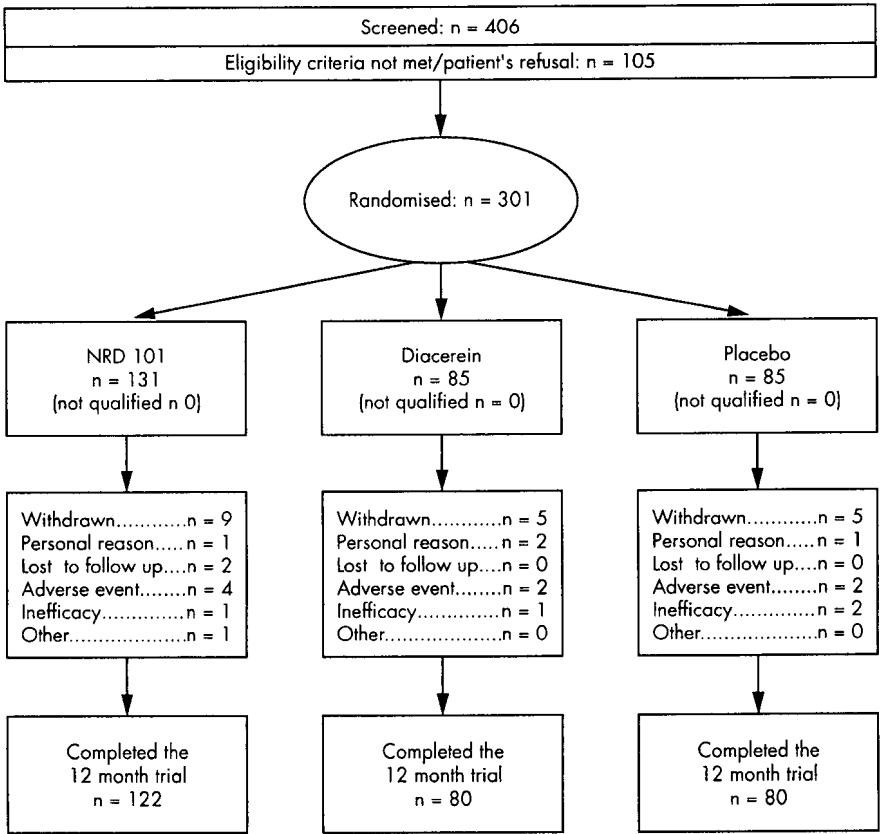


Figure 1 Course of the 20 month randomised trial.

Table 1 Baseline characteristics of the 301 randomised and treated patients with medial knee OA with regards to the treatment group

Baseline characteristics	NRD101 (n = 131)	Diacerein (n = 85)	Placebo (n = 85)
<i>Demographic characteristics</i>			
Age (years)	64.9 (8.4)	64.5 (7.8)	64.9 (7.7)
Sex (% female)	71.0	69.4	61.2
Weight (kg)	76.8 (14.0)	78.0 (13.9)	79.7 (14.5)
Height (cm)	164.1 (9.3)	162.9 (7.9)	163.5 (8.9)
Right knee, No (%)	65 (50)	41 (48)	48 (56)
<i>Symptomatic variables</i>			
Pain score on 0–100 VAS	61.7 (13.6)	59.6 (12.5)	59.1 (14.7)
Functional impairment (Lequesne's index)	11.1 (2.8)	10.5 (2.6)	10.5 (3.1)
Patient's global assessment (0–100 VAS)	59.7 (15.9)	59.0 (17.0)	57.3 (18.5)
Percentage of painful days during the previous month (0–100 VAS)	85.5 (20.4)	83.0 (18.5)	82.6 (21.0)
<i>Structural variables</i>			
Joint space width (mm)	(n = 127) 4.5 (1.2)	(n = 82) 4.5 (1.1)	(n = 83) 4.7 (1.3)
Osteophyte score (4 grades), No (%)	(n = 128)	(n = 84)	(n = 83)
0	5 (4)	4 (5)	5 (6)
1	53 (41)	41 (49)	36 (43)
2	59 (46)	31 (37)	40 (48)
3	11 (9)	8 (10)	2 (2)
Kellgren and Lawrence score (5 grades), No (%)	(n = 129)	(n = 84)	(n = 83)
0	1 (0.8)	0 (0)	0 (0.0)
1	4 (3)	3 (4)	2 (2)
2	30 (23)	12 (14)	19 (23)
3	90 (70)	66 (79)	60 (72)
4	4 (3)	3 (4)	2 (2)

Results are given as mean (SD) unless otherwise indicated.

washout period. Aspirin at an antiplatelet dose (<500 mg/day) was allowed. If non-steroidal anti-inflammatory drugs (NSAIDs) were required, the drugs used were those with an equivalent dosage available, and a 7 day washout period was required before each evaluation visit. No systemic corticosteroid, IA treatment (lavage, HA, corticosteroid), or any potential symptom modifying drug was allowed during the study.

Collected variables

Baseline evaluation

Age, sex, weight, height, past history of knee OA, and treatment were noted.

Symptomatic efficacy criteria

Pain on a 0–100 VAS, Lequesne's algofunctional index, patient's global assessment of disease activity (0–100 VAS), and percentage of painful days during the previous months (0–100 VAS) were collected at baseline, weeks 1, 2, 6, and months 4, 6, 8, 10, 12. Global assessments of the treatment efficacy by the patient and by the investigator (five level Likert scale) were noted at the end of the study. The use of concomitant treatments (analgesics, NSAIDs) was evaluated by the numbers of days of intake between each clinic visit.

Structural efficacy criteria

The structure of the OA knee was evaluated by radiography at baseline and at the final visit or at the end of the follow up. The x ray procedure was strictly standardised. Anteroposterior radiographs of the knee joints were obtained with patients in a weightbearing position, joint fully extended, standing at 1 m from the x ray source, with a constant and reproducible foot position using previously published guidelines^{21–22}: (a) the distance between the back of the knees and the plate was noted; (b) the feet were rotated 10° internally and the position of the feet outlined on a sheet of paper (foot map); (c) the central ray of the x ray beam was centred on the joint space and inclined downward to ensure

that the medial tibial plateau was parallel to the x ray beam. The angle of inclination was noted and reproduced on the final visit for radiography.

All films were centralised and duplicated for each observer (PD, PhR). At the end of the study the films of the same patient were analysed by the two observers who were unaware of the treatment, the sequence of radiographs, and the results of the other observer. The observer determined the location of the narrowest point of the JSW on the radiograph of a given knee (minimal JSW), then transferred this point to the other films of the set being measured, judging by eye. The anatomical limits for measurement of the JSW were the bone contour of the medial tibial plateau (the anterior side if the anterior and the posterior sides were not correctly aligned) and the bone contour of the medial femoral condyle. Both limits were marked with a short stroke of a dedicated pencil. The distance between these limits was measured with a 0.1 mm graduated magnifying glass. Each observer separately determined the narrowest point. The mean of the results of the two observers was the JSW measure used.

The intra- and interobserver reproducibilities were evaluated for the study and were considered to be acceptable: interobserver intraclass correlation coefficient 0.912 (0.887–0.931) and intraobserver (PD, PhR) intraclass correlation coefficient 0.996 (0.991–0.998) and 0.992 (0.989–0.996), respectively.

The observers also assessed the Kellgren and Lawrence grade of the femorotibial joints.²³ Osteophytes were assessed using the Altman atlas.²⁴

Evaluation of safety

During each visit, the investigators evaluated the safety measures. In addition, at the time of entry into the study and at the final visit, blood samples were collected to evaluate biological variables as well as liver and kidney functions. Global assessment of treatment safety by the investigator (five level Likert scale) was also recorded at baseline, months 4, 8, and 12.

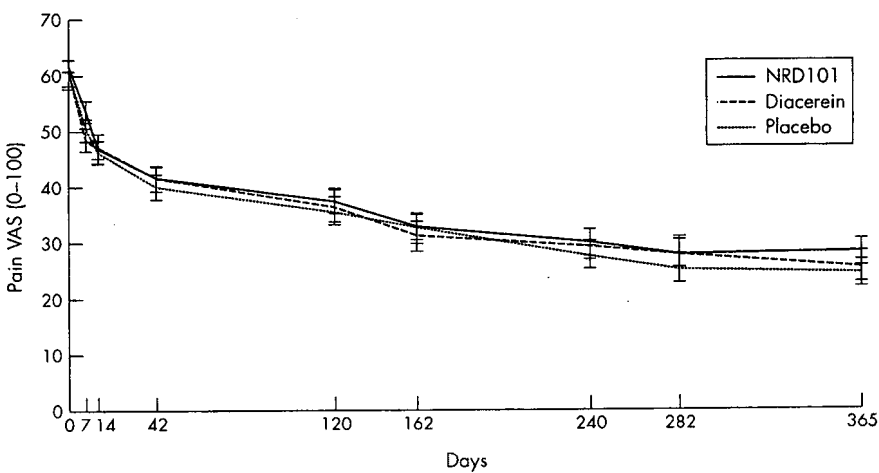


Figure 2 Change in pain VAS throughout the study according to treatment group.

Statistical analysis

Sample size calculation

It was calculated that the inclusion of 280 patients (120 in the HA group and 80 in each of the other groups) would be sufficient to demonstrate a difference, between baseline and 1 year of at least 15 mm with a standard deviation of 35 mm on the VAS pain scale between the active and the placebo groups, with an α risk of 0.05 and a power of 0.90 (two tailed test). Moreover, this sample size would also be sufficient to detect a difference of at least 0.40 mm with a standard deviation of 1 mm in JSW change from baseline to final visit between the groups ($\alpha = 0.05$, $\beta = 0.20$, two tailed test).

Symptomatic outcome measures

Analysis was made using an intention to treat approach, with the last observation carried forward. The main criterion for assessment of symptomatic efficacy was the pain VAS change between baseline and final visit. Symptomatic efficacy on pain was also evaluated with the following: area under the curve from baseline to final visit, percentage of patients with an improvement of at least 30% between baseline and final visit (percentage of responders), and change observed for each course of HA injections. The 30% cut off point was set arbitrarily before the study started. These analyses (change between baseline and final visit, area under the curve, percentage of responders, change by IA injection sequences) were also performed with Lequesne's algofunctional index and the patient's global assessment of disease activity, and the percentage of painful days during the previous month (variance analysis). The number of days on which analgesics or NSAIDs had been used was also assessed.

Structural outcome measures

Analysis was made using the data of the completer patients. The primary criterion for assessment of structural efficacy was the joint space narrowing (JSN) between baseline and the final visit. The second criterion was the percentage of patients with structural progression. This progression was defined by a JSN >0.50 mm during the study, as previously reported.^{3 5 25} Both analyses were made using a χ^2 test.

RESULTS

Patients

Of 406 screened patients, 301 were considered eligible for the study and were randomised (fig 1). The most common reason for non-inclusion was either a lack of radiographic evidence of knee OA or severe disease with a JSW <2 mm at the narrowest point. Of the 301 randomised patients, 19 did not complete the study, with roughly equal numbers of discontinuations, similar times to discontinuation, and similar reasons for withdrawal in each treatment arm (fig 1). At the end of the study, 9/124 (7%) patients in the NRD101 group, and 5/85 (6%) patients in both the diacerein group and the placebo group had discontinued the treatment.

The baseline knee radiograph was obtained in 292 patients and both radiographs (baseline and final) were obtained in 277 patients.

Table 1 summarises the main baseline characteristics of the 301 patients. The demographic, symptomatic and structural characteristics did not differ between the three groups.

Symptomatic efficacy criteria

Symptomatic outcome measures showed a significant improvement from baseline in the in the three treatment

Table 2 Evaluation of the treatment symptomatic efficacy between groups: changes between baseline and final visit. Intention to treat analysis with the last observation carried forward

Changes between baseline and final visit (n=301)	NRD101 (n=131)	Diacerein (n=85)	Placebo (n=85)	Analysis of variance (p value)
Pain (0-100 VAS)	-33.5 (28.5)	-33.9 (25.7)	-34.5 (27.4)	0.96
Lequesne's algofunctional index*	-20.0 (16.5)	-18.8 (14.7)	-18.9 (16.9)	0.84
Patient's global assessment (0-100 VAS)	-29.7 (26.9)	-32.8 (24.0)	-31.1 (31.7)	0.82
Percentage of painful days (0-100 VAS)	-43.5 (40.3)	-45.6 (37.8)	46.6 (37.2)	0.83

Results are shown as mean (SD).
*For change assessment, the 0-24 Lequesne's index has been translated into a 0-100 scale.

43

Table 3 Assessment of the treatment efficacy by the patient and investigator after 1 year's treatment, by treatment group								
	Assessment of treatment efficacy by the patient				Assessment of treatment efficacy by the investigator			
	NRD101	Diacerein	Placebo	Total	NRD101	Diacerein	Placebo	Total
Very good								
No	41	18	21	80	41	19	27	87
%	34	24	28	29.6	33	25	35	31.6
Good								
No	45	31	36	112	45	34	30	109
%	38	41	48	41.5	37	45	38	39.6
Moderate								
No	20	20	15	55	20	15	15	50
%	17	27	20	20.4	16	20	19	18.2
Bad								
No	11	3	2	16	14	5	4	23
%	9	4	3	5.9	11	7	5	8.4
Very bad								
No	3	3	1	7	2	2	2	6
%	3	4	1	2.6	2	3	3	2.2
Total No	120	75	75	270	122	75	78	275
	p=0.28 (Fisher's exact test)				p=0.79 (Fisher's exact test)			

groups. Between baseline and final visit, the mean (SD) change for pain VAS was -33.9 (27.3) mm (fig 2), for Lequesne's index (0-100 modified scale) -19.3 (16.1), for the patient's global VAS -31.0 (27.6) mm, and for the percentage of painful days -45.0 (38.7). However, no statistically significant difference was observed in the intention to treat or completer populations between the different groups (table 2). Similarly, no difference was seen in the consumption of analgesics and NSAIDs. The results were similar when each IA course was analysed separately (data not shown).

No significant difference was seen in the assessment of the treatment efficacy by the patient and by the investigator between the three treatment groups (p=0.28, p=0.79, respectively) (table 3).

Structural efficacy criteria

A significant deterioration in the JSW (mean (SD) -0.09 (0.55) mm, n = 277, p = 0.01) was seen during the study, but without any significant difference between the three groups (p = 0.82). The percentage of patients with a progression >0.5 mm was 17.7%, 18.9%, and 20.3% (p = 0.90) in the NRD101, diacerein, and placebo groups, respectively. No difference was seen in the Kellgren and Lawrence score and the osteophyte score between the groups.

Safety

The number of patients experiencing any adverse event was similar between the three treatment groups: 81.7%, 84.7%, and 81.2% in the NRD101, diacerein, and placebo groups, respectively (p = 0.76). Most of these events were mild to moderate in intensity. Table 4 summarises the most commonly seen adverse events. Patients in the NRD101 group had significantly more knee pain during or after IA injection (p = 0.0088), and patients treated with diacerein had more diarrhoea (p < 0.0001) and urine colouration (p = 0.0009) than patients of the other two groups. Eight patients withdrew from the study owing to adverse events: four, two, and two in the NRD101, diacerein, and placebo groups, respectively.

DISCUSSION

This 1 year, multicentre, randomised, placebo controlled study failed to demonstrate any statistically significant symptomatic or structural effect of NRD101, a new IA hyaluronic acid, compared with placebo or diacerein, an anti-osteoarthritic drug.

Several hypotheses can be suggested to explain the lack of efficacy of a potentially active treatment in such a clinical trial: the study design, a huge placebo response hiding a real treatment effect, and/or a lack of efficacy of the drug.

Table 4 Most common adverse events experienced during the 1 year study by treatment group				
Adverse event	NRD 101 (n = 131)	Diacerein (n = 85)	Placebo (n = 85)	p Value
Knee pain during or after IA injection	24	9	19	0.0088
Diarrhoea	9	41	8	<0.0001
Nausea, vomiting	4	5	5	0.73
Gastrolgia	4	8	5	0.43
Other gastrointestinal disorders	9	18	7	0.07
Respiratory system disorders (bronchitis, rhinitis...)	17	12	16	0.48
Influenza-like symptoms	3	5	5	0.80
Skin disorders	9	8	1	0.06
Central and peripheral nervous disorders (headache, vertigo...)	8	5	2	0.16
Urine colouration	0	7	0	0.0009

The percentage of patients is shown.

42

Firstly, concerning the study design itself—this trial was designed and conducted with good practice conditions.^{25 26} It was a three arm, randomised, double blind, placebo controlled trial, approved by an ethical committee. The pain and function outcome variables were similar to those used in other HA and diacerein studies^{27–29} which demonstrated a positive effect on pain and/or on function. The sample size was calculated before the study, and the number of patients in each arm was greater than most of the previous positive HA trials.

The x ray examination methodology was particularly careful, with: (a) verification of the entire set of baseline radiographs by the same observer (PhR), before inclusion, to ensure their quality. If the quality was unsatisfactory, the patient was not included in the study; (b) the x ray technique was carefully described in a booklet handed to each radiography centre. The technique aimed at obtaining films with a constant and reproducible position for each patient and for the x ray beam; (c) the two observers who analysed the films were unaware of the treatment group, the sequence of radiographs, and of the results of the other observer. Their inter- and intraobserver reproducibilities were evaluated before the clinical trial, and the coefficients of correlation were high.

Despite this careful x ray methodology, the study design has some limitations: (a) the extended x ray view choice may not be optimal for detecting narrowing compared with a semiflexed view, but at the time of the study start, the semiflexed view was not yet the preferred method; (b) the femoropatellar compartment was not taken into account in the study; (c) the study duration based on previous personal data might have been too short to demonstrate any structural change in the knee.

Secondly, a huge placebo response due to IA injection might operate quite independently of the injections, and be sufficient to skew the results of the three groups, swamping any difference between them. This hypothesis has already been proposed by Henderson *et al*,³⁰ who also published a negative randomised placebo controlled HA trial. It is well known that injectable treatments have a higher placebo effect than oral treatments. In the database used to elaborate the OARSI responder criteria, the placebo effect was dramatically more important for the patients treated with IA injections than for those treated with oral placebo.^{31 32} In the OARSI database the mean (SD) observed change in the 0–100 pain outcome variable between baseline and the final visit in the placebo group was –24 (40) mm for IA HA trials (n = 99) versus –4 (73) mm for the oral NSAID trials (n = 175). The observed placebo effect seen in our trial was clearly higher (–34.5 (27.4) mm for pain), although it appeared that, in comparison with previous studies, the patients treated with NRD101 in the present study obtained approximately the same pain relief as those in previous studies.^{18 33–36} This might explain our inability to demonstrate any difference between groups, particularly between the placebo group and the diacerein group.

Three randomised controlled trials have evaluated the efficacy and safety of diacerein in patients with hip or knee OA,^{3 10 11} with two of those trials showing that diacerein has significant symptomatic effectiveness on pain compared with placebo (n = 772).^{10 11} However, in the more recent trial, no statistically significant difference in the symptomatic variables between the diacerein group and the placebo group was found (n = 507).³

Lastly, the lack of demonstration of a symptomatic treatment effect might be explained by a real lack of efficacy of the tested new HA, NRD101. The pain relieving mechanism of IA injections of HA is unknown. Multiple mechanisms of action have been proposed to explain the therapeutic

efficacy of the hyaluronan agents, including effects on physical and biomechanical properties of the joint, effects on cartilage biosynthesis and degradation, anti-inflammatory effects, and a direct analgesic effect related to interaction with pain receptors.^{37–40} Several studies with various preparations of HA from different sources and of differing molecular weights have been conducted.^{14 36 41–43} Although the variances in molecular weight and other methodological variations in trial design make direct comparisons difficult, there is some evidence of long term pain reduction with IA HA versus placebo for up to 6 months after treatment (effect size ν placebo varying from 0.0 to 0.90).⁴⁴

One of the mechanisms of action discussed concerns the molecular weight of the HA compound used. The average molecular weight of NRD101 is 1.900 kDa. A first trial compared the efficacy of two different HA compounds with different molecular weights and it failed to demonstrate any difference in clinical efficacy between the two preparations evaluated (1.000 kDa ν 7.000 kDa).¹⁸ Furthermore, these preparations did not differ from placebo injections, as assessed by patient related outcome variables.

Another comparison between two different preparations of hyaluronan suggested a greater pain relieving effect of higher molecular weight HA (6.000 kDa) than of a lower molecular weight HA (0.75 kDa).⁴⁵ This study lacked a saline injection control group. Moreover, further analysis of the complete database of this trial (original four arm study) failed to demonstrate any benefit of the higher molecular weight HA over the two other comparator HA compounds (0.800 and 2.000 kDa) or the denatured control Synvisc preparation.⁴⁶

Our study failed also to demonstrate any structural efficacy of NRD101 and diacerein compared with placebo. The potential for structural modification by HA (Hyalgan) was first evaluated in a pilot prospective, controlled study of 1 year's duration of 36 patients with OA.⁴ After randomisation, either conventional treatment or three courses of three IA injections of Hyalgan were given at 3 month intervals, as in our study. Arthroscopic assessment showed decreased deterioration in structural variables in the Hyalgan treated group, suggesting that repeated IA injections might delay disease progression. However, this study failed to demonstrate any structural effects using JSW as outcome measure, although it did show a structural effect using two different arthroscopic grading systems.

A recent 1 year multicentre randomised placebo controlled, double blind trial evaluated structure modification in knee OA using IA injections of 0.500–0.730 kDa HA (Hyalgan). The change in the JSW between baseline and final visit was compared by analysis of variance. The mean (SD) loss in the HA group was –0.22 (1.1) and in the placebo group 0.60 (1.1) ($p < 0.05$), suggesting that the HA used had structural efficacy.⁴⁷ Using the same structural outcome variables and a careful radiographic methodology, we failed to show similar results.

Although treatment with diacerein for 3 years has shown a significant structure modifying effect as compared with placebo in the hip,³ we did not see any effect of this treatment in the knee after 1 year. In the ECHODIAH trial, radiographic progression of 0.5 mm was seen in 29.2% of patients receiving diacerein and 35.7% receiving placebo at the end of the first year. In comparison, in our study, the percentages of progressors were 18.9 and 20.3% in the diacerein and placebo groups, respectively. In view of these results, it might be suggested that OA progression may be easier to detect in the hip than in the knee.

In conclusion, this first controlled trial comparing a potential oral structure modifying drug with an IA anti-osteoarthritic drug in knee OA failed to demonstrate any benefit of these potentially symptomatic and structure

modifying drugs compared with placebo. The place of these treatments in the management of knee OA is still debated,^{48, 49} and further studies are needed.

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Evaluation of the symptomatic and structural efficacy of a new hyaluronic acid compound, NRD101, in comparison with diacerein and placebo in a 1 year randomised controlled study in symptomatic knee osteoarthritis

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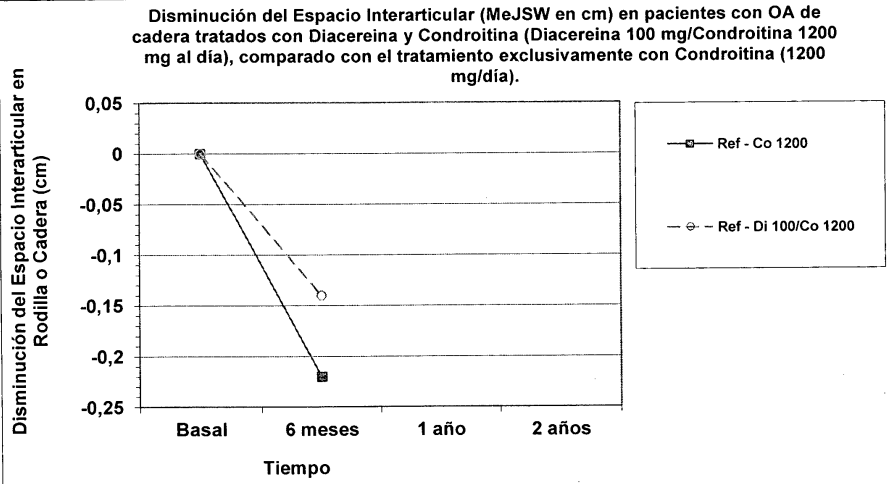
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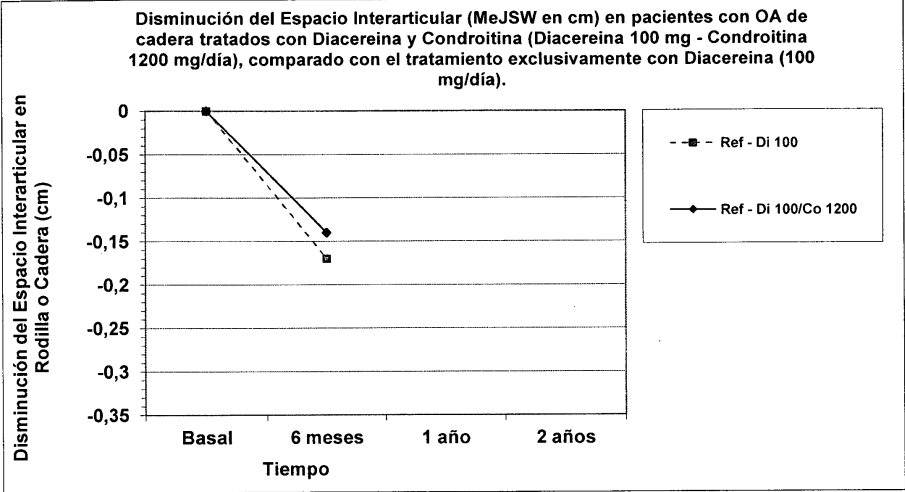
Cuadro 1. Comparación de la eficacia del tratamiento con Diacereina (100 mg/día) - Condroitina (1200 mg/día) y la combinación de ambos activos (Estudio de referencia de la solicitud de patente) en pacientes con OA de cadera. utilizando la prueba t de Student, para el cambio en MeJSW.

Estudio	Primer Autor	Tratamiento (Dosis en mg/día)	No. de Casos	Dura- ción Trata- miento	Cambio en MeJSW (cm) - 6 meses Promedio ± Desv.Est.
Estudio de Referencia	Grupo de Referencia	Ref - Di 100	40	6 meses	-0,17 ± 0,24
		Ref - Co 1200	40	6 meses	-0,22 ± 0,22
		Ref - Di 100/Co 1200	40	6 meses	-0,14 ± 0,20

TIEMPO DE TRATAMIENTO				
Tratamiento	Basal	6 meses	1 año	2 años
Ref - Co 1200	0,00	-0,22		
Ref - Di 100/Co 1200	0,00	-0,14		



TIEMPO DE TRATAMIENTO				
Tratamiento	Basal	6 meses	1 año	2 años
Ref - Di 100	0,00	-0,17		
Ref - Di 100/Co 1200	0,00	-0,14		



19