

Señor Superintendente
SUPERINTENDENCIA DE INDUSTRIA Y COME
E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 13-043214- -00013-0000

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Evento : 378
Actuación : 523

Referencia : Expediente No. **13.043.214**
Asunto : Solicitud de patente: **"COMPOSICIÓN FARMACÉUTICA MICROPARTICULADA QUE COMPRENDE ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS QUÍMICOS DEL MISMO, EN UNA MATRIZ DE COPOLÍMERO DE ÁCIDO POLI(LÁCTICO-CO-GLICÓLICO)"**
Solicitante : FLEXION THERAPEUTICS, INC.
Fecha de solicitud : 4 de Marzo de 2013

I. RECURSO VÍA GUBERNATIVA

Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad **FLEXION THERAPEUTICS, INC.** solicitante de la patente de la referencia, por el presente escrito atentamente manifiesto a usted que debidamente notificada de la Resolución No. **11339** del 13 de Marzo de 2015, interpongo en su contra el recurso de **REPOSICIÓN**, para que sea revocada y en consecuencia se conceda el privilegio de patente de invención para **"COMPOSICIÓN FARMACÉUTICA MICROPARTICULADA QUE COMPRENDE ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS QUÍMICOS DEL MISMO, EN UNA MATRIZ DE COPOLÍMERO DE ÁCIDO POLI(LÁCTICO-CO-GLICÓLICO)"** a favor de **FLEXION THERAPEUTICS, INC.**

II. OPORTUNIDAD DE LA IMPUGNACIÓN

La Resolución No. **11339** del 13 de Marzo de 2015, con fecha de publicación listado del 17 de Marzo de 2015, fecha de vencimiento del 17 de Abril de 2015, y fecha del término legal 4 de Mayo de 2015.

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III. LA DECISIÓN RECURRIDA

- 3.1 Mediante la Resolución objeto de la presente impugnación, el Superintendente de Industria y Comercio decidió:
- 3.1.1 Denegar la patente de invención a la creación titulada: **“COMPOSICIÓN FARMACÉUTICA MICROPARTICULADA QUE COMPRENDE ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS QUÍMICOS DEL MISMO, EN UNA MATRIZ DE COPOLÍMERO DE ÁCIDO POLI(LÁCTICO-CO-GLICÓLICO)”**.
- 3.2 En la parte motiva de la providencia, se mencionaron los siguientes fundamentos:
- 3.2.1 Mediante escrito radicado bajo el no. 13-043214-00009-0000 del 23 de Enero de 2015, respondió oportunamente el requerimiento formulado y presentó nuevas reivindicaciones 1 a 7 que reemplazan las originalmente presentadas. Se aceptó el nuevo pliego reivindicatorio presentado, como quiera que se ajusta a las prescripciones contenidas en el artículo 34 de la Decisión 486.
- 3.2.2 Las reivindicaciones 1 a 7, no cumplen con el requisito de nivel inventivo.

IV. OBJETO DEL RECURSO

De acuerdo con los argumentos que expongo a continuación, solicito atentamente a su Despacho lo siguiente:

1. Revocar la Resolución No. **11339** del 13 de Marzo de 2015.
2. Conceder el privilegio de patente de invención para **“COMPOSICIÓN FARMACÉUTICA MICROPARTICULADA QUE COMPRENDE ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS QUÍMICOS DEL MISMO, EN UNA MATRIZ DE COPOLÍMERO DE ÁCIDO POLI(LÁCTICO-CO-GLICÓLICO)”** a favor de **FLEXION THERAPEUTICS, INC.**

V. PRESENTACIÓN DE UNA SOLICITUD DIVISIONAL Y MODIFICACIÓN DE UNA SOLICITUD EN TRÁMITE

En virtud del Artículo 36 de la Decisión 486 mediante el cual se establece la posibilidad de dividir la solicitud en dos o más fraccionarias, se presenta en esta oportunidad una solicitud divisional, junto con un pliego reivindicatorio conformado por 6 reivindicaciones, donde en la solicitud original se encuentran las reivindicaciones relacionadas con una formulación inyectable que comprende (a) micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA) o un análogo químico o una sal farmacéuticamente aceptable del mismo y una matriz de copolímero de ácido poli(láctico-co-glicólico) (PLGA), en donde el TCA comprende entre 22% a 28% de las micropartículas y en donde el copolímero de PLGA tiene las siguientes características: (i) un peso molecular en el rango de 40 a 70 kDa; y (ii) una relación molar de lacturo:glicoluro de 80:20 a 60:40, mientras que en la solicitud divisional las reivindicaciones se refieren a una formulación como la de la solicitud parental, que presenta un diámetro medio de macropartículas entre 10 µm a 100 µm contenidas en el pliego reivindicatorio presentado junto con la respuesta a la acción oficial No. 11619, presentado el 23 de Enero de 2015.

Teniendo en cuenta que se cumplen con los requerimientos exigidos por el artículo mencionado, se solicita atentamente dar trámite a esta solicitud divisional.

Por otra parte, de acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 6 reivindicaciones.

Por lo tanto, los argumentos esgrimidos a continuación con respecto a la patentabilidad de la invención, en los términos del capítulo reivindicatorio modificado y del pliego reivindicatorio de la solicitud divisional, resultan plenamente predicables del capítulo reivindicatorio sobre el cual la patente fue negada. En efecto, la no ampliación de la materia en el nuevo pliego es evidencia suficiente de que el presente recurso controvierte el análisis de patentabilidad efectuado por su Despacho, de tal manera que el presente recurso cumple con los requisitos de ley para su aceptación y trámite.

VI. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, toda vez que la presente solicitud sí cumple con los requerimientos de novedad y nivel inventivo exigidos en la Decisión 486, como se demostrará a continuación:

6.1 La presente solicitud sí tiene nivel inventivo

A pesar de lo anterior y con el fin de demostrar que la presente solicitud cumple no sólo con el requerimiento de novedad sino también con el requerimiento de nivel inventivo, se pone de presente lo siguiente:

El artículo 18 de la Decisión 486 señala lo siguiente:

“Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica”.

Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

Respecto a lo anterior, el Tribunal de Justicia de la Comunidad Andina ha expuesto en la Interpretación Prejudicial del proceso 13-IP-2010:

“En este orden de ideas, se puede concluir que una invención goza de nivel inventivo cuando a los ojos de un experto medio en el asunto de que se trate, se necesita algo más que la simple aplicación de los conocimientos técnicos en la materia para llegar a ella, es decir, que de conformidad con el estado de la técnica el invento no es consecuencia clara y directa de dicho estado”.

[señalado fuera del texto]

Por lo anterior, se entiende que para que una persona medianamente versada en la materia pudiera derivar de manera obvia una invención, requeriría simplemente aplicar sus conocimientos técnicos. En contraste, todo aquello que va más allá de la simple aplicación de los conocimientos técnicos y que no ha sido revelado en el estado de la técnica, debe ser considerado inventivo.

A este respecto, respetuosamente solicitamos atentamente la reconsideración de las razones por las cuales se decidió negar la patente, con base en la siguiente información:

Traemos de presente que a la luz del requisito de nivel inventivo, no existe ninguna enseñanza o sugerencia en el estado del arte para que una persona versada en la materia estuviese motivada a sustituir el corticosteroide TCA por una proteína, como lo es la insulina, en las micropartículas de PLGA que son reveladas en los ejemplos del documento D1, toda vez que estos dos compuestos activos presentan diferentes estructuras, diferentes pesos moleculares (TCA: 435.5 g/mol e Insulina: 5808 g/mol) y diferentes propiedades químicas, características suficientes para presentar una actividad significativamente diferente.

Reiteramos que D1, tampoco, presenta sugerencias claras y específicas de qué tipo de polímero usar, el peso molecular del mismo y la relación molar de lactida: glicólido, como lo afirmar el señor Examinador. Recordemos que D1 no menciona una matriz de copolímero de PLGA, en el que PLGA tenga (i) un peso molecular en el intervalo de 40 a 70 kDa; y (ii) una relación molar de ácido láctico: ácido glicólico de 80:20 a 60:40, y se encuentra lejos de enseñar los intervalos tal cual son reclamados en la presente solicitud.

Por su parte, con base a las enseñanzas de D2, una persona versada en la materia que pretende producir formulaciones de micropartículas de liberación controlada o sostenida, no tendría ninguna razón objetiva para utilizar estas enseñanzas, ya que no da a conocer micropartículas de liberación controlada o sostenida de ningún tipo. De hecho, D2 enfatiza repetidamente que las formulaciones descritas, preferiblemente liberan una mayoría del agente farmacéutico encapsulado de las micropartículas a las 24 horas después de la administración (Resumen, párrafos [0010], [0029], [0044], [0140] y reivindicaciones 2, 3, 19, 20, 31, 34, 41, y 42). En consecuencia, una persona versada en la materia no habría sido motivada para combinar las enseñanzas de D1 y D2.

Además, D2 describe también rangos extremadamente amplios de los componentes de micropartículas y agentes activos, pero no hay evidencias objetivas que llevarían a un experto en la materia a los intervalos reivindicados. Por ejemplo, en los párrafos [0064] a [0077], D2 enumera una multitud de materiales potenciales de matriz, incluyendo PLGA, pero no hay ninguna revelación a un rango adecuado la relación molar de ácido láctico: ácido glicólico en las micropartículas de PLGA. De hecho, los ejemplos incluyen PLGA, pero no revelan el peso molecular o la relación molar de ácido láctico: ácido glicólico de los copolímeros utilizados. Por lo tanto, no hay razón alguna para que una persona versada en la materia seleccionara los rangos específicos de peso molecular y relación molar de ácido láctico: ácido glicólico mencionados por las reivindicaciones modificadas.

Nuevamente, queremos poner de presente los datos de dos expertos en la materia, como lo son el Doctor LeBlanc y el Doctor Kumar, que ya fueron presentados, donde afirman que las formulaciones de micropartículas TCA reclamadas no habrían sido obvias para el experto en la materia debido a que, como se ha explicado, muestran resultados sorprendentes e inesperados. Por lo tanto, la combinación específica de elementos e intervalos mencionados por la presente solicitud no es sólo la optimización de rangos. Dado que características como la velocidad de liberación y la velocidad de degradación dependen en gran medida el agente activo específico utilizado, se seleccionaron estos rangos específicos, ya que proporcionan un perfil de liberación sostenida deseado, a saber, la capacidad de entregar TCA a niveles terapéuticos sostenidos sin supresión del eje hipotalámico-pituitario-adrenal (HPA) durante al menos 14 días.

Las formulaciones de micropartículas con este perfil de liberación deseado han sido demostradas en estudios clínicos para proporcionar un efecto analgésico

clínicamente significativo, por ejemplo, alivio del dolor, durante todo el estudio de 12 semanas, y este efecto es una mejora significativa sobre una suspensión inyectable aprobada de TCA (IR TCA). Además, la declaración de Anjali Kumar, Ph.D., FAHA, demuestra que las formulaciones de micropartículas de TCA que se encuentran fuera de los intervalos reivindicados no presentan este perfil de liberación deseado.

Por ejemplo, la declaración Kumar demuestra que las formulaciones de micropartículas de PLGA utilizando una dosis de carga de TCA que fue menor que el intervalo reivindicado, de 22% a 28%, exhibía un perfil de liberación lenta con una liberación significativa acumulada menor por más de 28 días que la formulación reivindicada, mientras que las formulaciones de micropartículas de PLGA que tiene una dosis de carga de 40%, mostraron un perfil de liberación más rápido, con más del 80% de la TCA siendo liberada por 7 días después de la administración.

Además, la Declaración Kumar demuestra que las formulaciones de micropartículas hechas con un copolímero de PLGA que tiene una relación de ácido láctico a ácido glicólico fuera del intervalo reivindicado, es decir de 80:20 a 60:40, exhiben varias propiedades indeseables. Por ejemplo, las formulaciones de micropartículas hechas usando un copolímero de PLGA 50:50, liberan TCA a un ritmo más lento y tienen una liberación incompleta en comparación con la cantidad equivalente de TCA incorporado en una micropartícula hecha usando un copolímero PLGA 75:25 (es decir, dentro de la relación molar reclamada por las reivindicaciones modificadas). Además, las formulaciones de micropartículas hechas con el copolímero de PLGA 50:50 también mostraron una fase sustancial de retraso, con muy poca o ninguna TCA están siendo liberados después de 7 días, que continuaron hasta aproximadamente el día 50. Por último, la Declaración Kumar demuestra que se encontró que las formulaciones de micropartículas hechas usando un copolímero PLGA 75:25 que tienen un peso molecular menor que el intervalo reivindicado de 50-54 kDa, presentan una tasa de liberación de TCA más lenta y una liberación incompleta de TCA.

Así mismo, las formulaciones reivindicadas exhiben una jeringabilidad deseable, como se describe en la solicitud PCT. Los efectos secundarios adversos asociados con técnicas de encapsulación, tales como la presencia de aglomeración de micropartículas dentro de la población pueden conducir a la obstrucción de la aguja durante el retiro y la administración de formulaciones de micropartículas. Antes de la presentación de la solicitud, las formulaciones de micropartículas generalmente requerían agujas de calibre relativamente grandes y un largo tiempo de suspensión para evitar la obstrucción de la

aguja, que puede conducir a una dosis insuficiente de los productos y a la necesidad de reinyección. Por otra parte, las agujas de calibre grande son menos cómodas para los pacientes que reciben estas inyecciones, y las molestias asociadas con la inyección pueden llevar al paciente al no cumplimiento del régimen terapéutico debido al dolor.

La jeringabilidad de las micropartículas reivindicadas es una mejora sobre el estado de la técnica para encapsular micropartículas. Las micropartículas de la invención reivindicada forman soluciones de flujo libre y no aglomeradas que son adecuadas para la administración a través de agujas de calibre pequeño. La jeringabilidad de una formulación de micropartículas es un avance tecnológico sobre el estado de la técnica y no es meramente la optimización de rutina de una característica de las formulaciones de micropartículas reivindicadas.

En contraste, D1 no describe que las formulaciones de micropartículas son adecuados para la inyección mediante una aguja de calibre pequeño. D2 se refiere únicamente a la entrega por inhalación/respiratoria; por lo tanto, una persona versada en la materia que estuviese interesada en hacer formulaciones inyectables no tendría ninguna razón objetiva para utilizar las enseñanzas de D2. Por lo tanto, la invención reivindicada es un avance tecnológico sobre el estado de la técnica.

Adicionalmente, para el momento de presentación de la solicitud, ésta también presenta un avance tecnológico sobre el estado del arte en cuanto al cuidado de la osteoartritis, como se puede observar en uno de los adjuntos, donde las micropartículas de TCA/PLGA reclamadas están en ensayos clínicos en los Estados Unidos bajo el nombre del producto: FX006.

Estos estudios, particularmente la Fase 2b del ensayo clínico descrito en el resumen adjunto realizado por Bodick *et al.*, han demostrado que en los pacientes con dolor de osteoartritis moderado a severo, FX006 ofrece clínicamente una mejoría en el alivio del dolor significativa y representativa en comparación con el actual estándar de tratamiento para la artritis, una formulación de liberación inmediata de los TCA (TCA-IR) que se comercializa como Kenalog®. Por otra parte, los datos proporcionados en los ejemplos de la presente solicitud también demuestran un perfil de liberación superior para FX006 en comparación con la formulación TCA-IR (Kenalog®), como es posible observar en el documento adjunto en un modelo animal de la osteoartritis similar, que demuestra que la liberación sostenida de TCA seguida de una inyección intra-articular de FX006 prolonga significativamente el alivio del dolor en comparación con TCA-IR (Kenalog®).

Por lo tanto, FX006 fue específicamente diseñado para hacer frente a las limitaciones de las terapias intra-articulares actuales como Kenalog® proporcionando larga duración y analgesia local evitando efectos secundarios sistémicos.

Por lo tanto, las referencias citadas, solas o en combinación, no describen o sugieren los elementos específicos de las formulaciones de TCA reivindicadas. Como tal, no hay ninguna razón u otra evidencia proporcionada por las enseñanzas de D1 y D2 que llevarían el experto en la materia a la invención reivindicada. En consecuencia, se pone de presente que las formulaciones de micropartículas TCA reclamadas por las reivindicaciones modificadas no son obvias a la vista de los documentos citados y el estado de la técnica en el momento de presentación de la solicitud. Esto es apoyado por la amplitud de los intervalos descritos en D1 y D2, y la especificidad de los intervalos reivindicados, que se encuentran suficientemente lejos de los rangos revelados en los ejemplos de D1 y D2. Las diferencias son claras cuando los perfiles de liberación obtenidos por medio de la invención reivindicada se comparan con los ejemplos de D1.

Por lo tanto, es claro que las micropartículas reclamadas no están descritas en su totalidad, ni son sugeridas por D1 y/o D2, y los datos mencionados en el capítulo descriptivo son suficientes para apoyar la conclusión de que las formulaciones de macropartículas reclamadas demuestran resultados sorprendentes e inesperados que podrían no haberse previsto con base a las enseñanzas de D1, y que como bien menciona la "GUÍA PARA EXAMEN DE SOLICITUDES DE PATENTE DE INVENCION Y MODELOS DE UTILIDAD" de su despacho en el numeral 2.13.5.3.1, está reconocido como un indicio de nivel inventivo. Por consiguiente, se le debe otorgar una compensación a mi representada que demuestre nuevos hechos (efectos sorprendentes e inesperados) a las enseñanzas descritas en el estado de la técnica y que contribuyen con el desarrollo de la tecnología.

Por lo tanto, un técnico con conocimientos medios en la materia no estaba en condiciones de plantearse el problema, tampoco de resolverlo en la forma en que se reivindica y tampoco de prever el resultado, por lo que la presente solicitud posee la altura inventiva para que se le conceda el privilegio solicitado.

6.2 Concesión de Solicitudes equivalentes

Aunque compartimos la opinión de su Despacho, en cuanto a que la concesión de una solicitud de patente en otros países, equivalente a la solicitud Colombiana, no obliga a su Despacho a otorgar el privilegio de patente para la misma invención, sí constituye un antecedente favorable para el estudio de patentabilidad que respetuosamente solicitamos tener en cuenta. Por lo tanto, informamos a su Despacho que la presente invención ha sido otorgada en los siguientes países u oficinas de patentes de Estados Unidos y de Nueva Zelanda.

A este respecto, deseamos poner de presente que si bien cada país es autónomo de conceder o negar una solicitud luego de la realización del estudio de fondo, es claro que el hecho de que la novedad y el nivel inventivo de una invención hayan sido reconocidos por varias oficinas a nivel mundial, es un indicio de la patentabilidad de la misma toda vez que (i) el estudio de novedad y nivel inventivo en todas las Oficinas de Patentes del mundo es realizado por personas con conocimientos técnicos en el área de interés que son consideradas personas idóneas para emitir conceptos sobre la patentabilidad de una invención y que (ii) los resultados de los exámenes de novedad o de patentabilidad efectuados respecto a solicitudes extranjeras pueden ser reconocidos como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención, tal como se señala en el artículo 46 de la Decisión 486:

“Artículo 46.- La oficina nacional competente podrá requerir el informe de expertos o de organismos científicos o tecnológicos que se consideren idóneos, para que emitan opinión sobre la patentabilidad de la invención. Asimismo, cuando lo estime conveniente, podrá requerir informes de otras oficinas de propiedad industrial.

De ser necesario, a efectos del examen de patentabilidad y a requerimiento de la oficina nacional competente, el solicitante proporcionará, en un plazo que no excederá de 3 meses, uno o más de los siguientes documentos relativos a una o más de las solicitudes extranjeras referidas total o parcialmente a la misma invención que se examina:

a) copia de la solicitud extranjera;

b) copia de los resultados de exámenes de novedad o de patentabilidad efectuados respecto a esa solicitud extranjera;

(...)

La oficina nacional competente podrá **reconocer los resultados de los exámenes referidos en el literal b) como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad de la invención** (Negrilla fuera del texto).

Conclusión

El documento D, el documento D2, o su combinación no resulta anterioridad válida capaz de afectar la novedad y el nivel inventivo de la invención de la presente solicitud.

Por todo lo anterior, consideramos que la presente solicitud cumple a cabalidad con los requerimientos de patentabilidad exigidos por la legislación actual, por lo que atentamente solicitamos en consideración lo siguiente:

VII. PETICIÓN

Por todo lo anterior, solicito a ese Despacho lo siguiente:

7.1 Que al considerar las razones precedentes se revoque la decisión contenida en la Resolución No. **11339** del 13 de Marzo de 2015, en cuanto resuelve negar el privilegio de patente de invención.

7.2. Que se acepte el nuevo pliego reivindicatorio presentado con este escrito, conformado por 6 reivindicaciones.

7.3. Que se otorgue el privilegio de patente de invención para **“COMPOSICIÓN FARMACÉUTICA MICROPARTICULADA QUE COMPRENDE ACETÓNIDO DE TRIAMCINOLONA O ANÁLOGOS QUÍMICOS DEL MISMO, EN UNA MATRIZ DE COPOLÍMERO DE ÁCIDO POLI(LÁCTICO-CO-GLICÓLICO)”** a favor de **FLEXION THERAPEUTICS, INC.**

VIII. NOMBRE Y DIRECCIÓN

El nombre y la dirección del solicitante recurrente son los siguientes:

FLEXION THERAPEUTICS, INC.

300 Trade Center, Suite 2460, Woburn,
Massachusetts 01801,
Estados Unidos de América

IX. ANEXOS

- Formulario de modificaciones en solicitud pendiente.
- Recibo por concepto de presentación de modificaciones a las reivindicaciones por un valor de \$132.000.
- Nuevo pliego reivindicatorio conformado por 6 reivindicaciones.
- Solicitud de división de una solicitud en trámite.
- Memoria descriptiva de la solicitud divisional.
- Pliego reivindicatorio divisional conformado por 6 reivindicaciones.
- Comprobante de tasa por la solicitud divisional por valor de \$478.000.
- Copia del Poder.
- Ensayos clínicos en los Estados Unidos bajo el nombre del producto: FX006.
- Patente estadounidense No. 8828440 B2.
- Certificado de otorgamiento de la Oficina de Patentes de Nueva Zelanda.
- Kumar, a; Bendele, A. Blanks, R., Bodick, N. Sustained efficacy of a single intra-articular dose of FX006 in a rat model of repeated localized knee arthritis. Osteoarthritis Research Society International, 2014.
- Bodick, N., ACR Concurrent Abstract Session Osteoarthritis I: Therapeutics in osteoarthritis. 2013.

X. NOTIFICACIONES

Atentamente manifiesto a usted que recibiré notificaciones en la Secretaria de su Despacho o en mi oficina de abogada situada en la Carrera 4ª. No. 72-35, piso 4º, de esta ciudad de Bogotá, D.C.

Señor Superintendente,

LUZ CLEMENCIA DE PÁEZ
LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

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No. M-2015-279879\CPT

 Industria y Comercio SUPERINTENDENCIA	Espacio reservado para el adhesivo de radicación
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DIRECCIÓN DE NUEVAS CREACIONES
MODIFICACIONES Y/O CORRECCIONES

1. Identificación del Trámite

☐ Error material

☒ Modificación a una Solicitud en trámite

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Registro de Diseño Industrial

☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural

☐

Persona Jurídica

☒

FLEXION THERAPEUTICS, INC.

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa Micro ☐ Pequeña ☐ Mediana ☐ Otra ☐

Documento de identificación: ☐ C.C. ☐ C.E. ☐ NIT ☐ Otro Número _____

Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
Estado de Delaware, Estados Unidos de América	300 Trade Center, Suite 2460, Woburn 01801, Massachusetts, Massachusetts	Woburn
Dirección electrónica	No. Fax	Número telefónico
clientes@cavelier.com	2 11 86 50	3 47 36 11

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

Apellidos y Nombre
De Páez Luz Clemencia

Documento de identificación
C.C. 35.456.344

Tarjeta profesional
T.P.A. 23.555

Dirección y domicilio	Ciudad	
Carrera 4ª No. 72 –35	Bogotá	
Dirección electrónica	No. Fax	Número telefónico
cavelier@cavelier.com	2 11 86 50	3 47 36 11

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general

4. Datos del trámite

Corrección:

Expediente No 13.043.214

Aparece

Debe ser

Modificación:



Modificación al capítulo reivindicatorio.

Presento nuevo capítulo reivindicatorio compuesto por 6 reivindicaciones y pido respetuosamente que el examen de patentabilidad sea realizado sobre estas nuevas reivindicaciones presentadas. Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y además se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

5. Anexos



Comprobante de pago de la tasa para la presentación de la corrección y/o modificación por \$132000.



Poder, si fuere el caso.



Documento que contiene las modificaciones o correcciones.



Copia de la solicitud y sus anexos en formato magnético.



Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por.

6. Firma

Nombre y apellidos

LUZ CLEMENCIA DE PAEZ

C.C: 35.456.344 DE Usaqué

Firma

Luz Clemencia de Paez

Tarjeta Profesional 23.555

mgm

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 Industria y Comercio SUPERINTENDENCIA	Espacio reservado para el adhesivo de radicación
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DIRECCIÓN DE NUEVAS CREACIONES
CONVERSIÓN, DIVISIÓN Y FUSIÓN DE SOLICITUDES

1. Identificación del Trámite

☐ Conversión

☒ División

☐ Fusión

☒ Patente de Invención

☐ Patente de Modelo de Utilidad

☐ Registro de Diseño Industrial

☐ Esquema de Trazado de Circuitos Integrados

2. Datos del solicitante

Persona Natural☐

Persona Jurídica☒

FLEXION THERAPEUTICS, INC.

Nombre o denominación / Nombre o razón social completa

Nombre representante legal

Tipo de empresa

Micro☐

Pequeña☐

Mediana☐

Otra☐

Documento de identificación:

☐ C.C.

☐ C.E.

☐ NIT

☐ Otro Número

Nacionalidad/País de constitución	Dirección y domicilio del titular	Ciudad
Estado de Delaware, Estados Unidos de América	300 Trade Center, Suite 2460, Woburn 01801, Massachusetts, Massachusetts	Woburn
Dirección electrónica	No. Fax	Número telefónico
clientes@cavelier.com	2 11 86 50	3 47 36 11

☐ Autorizo expresamente a la Superintendencia de Industria y Comercio para que todas las comunicaciones sean enviadas a través de la dirección de correo electrónico

3. Datos del apoderado:

Apellidos y Nombre

Documento de identificación

Tarjeta profesional

De Páez Luz Clemencia

C.C. 35.456.344

T.P.A. 23.555

Dirección y domicilio	Ciudad	
Carrera 4ª No. 72 –35	Bogotá	
Dirección electrónica	No. Fax	Número telefónico
cavelier@cavelier.com	2 11 86 50	3 47 36 11

En caso de haber presentado poder general para asuntos que se adelanten ante la Delegatura de Propiedad Industrial, sírvase indicar el número de su radicación o protocolo de poder general

4.

Datos del trámite

CONVERSION

Expediente _____

De: _____
A: _____

DIVISION

Expediente : **13.043.214**
De: _____
A: _____

FUSION

Expediente _____

De: _____
A: _____

5.

Comprobante de pago No. 15-0049667 Fecha: 2015/05/04

6.

Anexos

☒

Comprobante de pago de la tasa de presentación solicitud por \$478.000.

☐

Comprobante de pago por reivindicaciones adicionales después de la décima reivindicación por

☒

Poder, si fuere el caso con el que se acredita la representación

☒

Documento que contiene la conversión, división o fusión de la solicitud

☐

Copia de la solicitud y sus anexos en formato magnético

7. Firma	
Nombre y apellidos	Firma
LUZ CLEMENCIA DE PAEZ	<i>Luz Clemencia de Paez</i>
C.C. 35.456.344 DE Usaquén	Tarjeta Profesional 23.555

mgm CPT\SDC\ID-AF279913\WPC20037

NOTA: Esta es una solicitud de división de la materia contenida originalmente en la solicitud de patente No. **13.043.214**. La solicitud de división de la materia se hace como consecuencia de la decisión proferida por ese Despacho por medio de la resolución No. 11339 del 13 de marzo de 2015. Por lo tanto pido que esta solicitud de división de materia sea tratada con el beneficio de presentación de la solicitud original, esto es 4 de marzo de 2013 y la prioridad que allí se reivindica el 4 de agosto de 2010.

Nota: La copia básica original se encuentra en el expediente No. **13.043.214**

REIVINDICACIONES MODIFICADAS

1. Una formulación inyectable que comprende (a) micropartículas de liberación controlada o sostenida que comprenden acetónido de triamcinolona (TCA) o una sal farmacéuticamente aceptable del mismo y una matriz de copolímero de ácido poli(láctico-co-glicólico) (PLGA), en donde el TCA comprende entre 22% a 28% de las micropartículas y en donde el copolímero de PLGA tiene las siguientes características: (i) un peso molecular en el rango de 40 a 70 kDa; y (ii) una relación molar de lacturo:glicoluro de 80:20 a 60:40.
2. La formulación de la reivindicación 1, en donde el copolímero de PLGA tiene una relación molar de ácido láctico: ácido glicólico de 75:25.
3. La formulación de la reivindicación 1, en donde el TCA comprende una dosis de carga total de TCA entre 10 a 50 mg.
4. La formulación de la reivindicación 1, en donde el copolímero de ácido láctico-ácido glicólico tiene una viscosidad intrínseca en el rango de 0.38 a 0.42 dL/g.
5. La formulación de la reivindicación 1, en donde las micropartículas comprenden adicionalmente una unidad estructural de polietilenglicol (PEG), en donde la unidad estructural de PEG comprende entre 25% a 0% de porcentaje en peso de la micropartícula.
6. Un proceso de obtención para fabricar la formulación de la reivindicación 1, en donde las micropartículas se fabrican utilizando un proceso de evaporación de solvente, utilizando por lo menos un aparato de secado por aspersión, aparato de lecho fluido o un disco giratorio, en donde el TCA se dispersa en una solución orgánica de copolímero de ácido láctico-ácido glicólico y la mezcla se trata para retirar el solvente de la mezcla, produciendo por lo tanto micropartículas.

Conclusion: The fast-track pathway leads to a reduction in irreversible sight loss and is associated with reduced diagnosis and treatment costs. It results in 2.6 QALY's gained for each patient that does not suffer sight loss, suggesting that the fast-track pathway is more cost effective than the conventional pathway for management of early GCA. The ICER of implementing the fast-track pathway is $\leq 1,950$ per QALY with an average cost saving to the NHS of ≤ 925 for each patient. Our results do not include the small educational/refresher costs and are preliminary but indicate that the Fast track GCA pathway should be 'rolled out' globally.

Disclosure: K. Achilleos, None; P. Patil, None; W. W. Maw, None; L. Bown, None; D. Halsall, None; C. Dobson, None; C. DeJaco, None; F. Borg, None; S. Gupta, None; B. Dasgupta, None.

ACR Concurrent Abstract Session
Osteoarthritis I: Therapeutics in Osteoarthritis
Tuesday, October 29, 2013, 2:30 PM-4:00 PM

2668

A Randomized, Double-Blind, Dose Ranging Study Comparing FX006, An Intra-Articular (IA) Sustained-Release Formulation Of Triamcinolone Acetonide (TCA), To An Approved Injectable Suspension Of TCA In Patients With Osteoarthritis (OA) Of The Knee. Neil Bodick¹, Joelle Lufkin¹, Christina Willwerth¹, Pierre Lachance², Gregory Jassey³, Anil Gupta⁴, Anthony Chris⁵, Marc Russo⁶, Michael O'Mahony⁷, Sam Hencin⁸, Louise Murdoch⁹, Ferdinandus de Looze¹⁰, David Hunter¹¹ and Michael Clayman¹. ¹Flexion Therapeutics, Burlington, MA, ²Clinique St-Louis (Recherche) Inc, Quebec, QC, ³North Walkerville Orthopaedic Associates, Windsor, ON, ⁴Anil K. Gupta Medicine Professional Corporation, Toronto, ON, ⁵Aim Health Group, Waterloo, ON, ⁶Hunter Clinical Research, Broadmeadow, Australia, ⁷London Road Diagnostic Clinic and Medical Centre, Sarnia, ON, ⁸SKDS Research Inc., Newmarket, ON, ⁹Emeritus Research, Malvern East, Australia, ¹⁰AusTrials Pty Limited, Sherwood, Australia, ¹¹Royal North Shore Hospital, St. Leonards, Australia.

Background/Purpose: FX006 is a novel sustained-release formulation of TCA in poly(lactic-co-glycolic) acid microspheres intended to maintain therapeutic concentrations in the joint up to 3 months following IA injection. In patients (pts) with OA of the knee, FX006 was compared to an approved injectable suspension of TCA (TCA IR) to identify a dose of FX006 to move forward into Phase 3.

Methods: Pts with baseline average daily pain intensity (ADP) of ≥ 5 to ≤ 9 on an 11 point Numeric Rating Scale (NRS) ranging from 0 (no pain) to 10 (pain as bad as you can imagine) were randomized (1:1:1:1) and treated with a single IA injection of FX006 (containing 10, 40 or 60 mg of TCA) or 40 mg of TCA IR. Pts were evaluated at 7 visits over 12 wks for efficacy, safety and PK. Primary endpoint: change from Baseline to each of Wks 8, 10 and 12 in the weekly mean of ADP. Secondary endpoints: time to onset of pain relief, WOMAC (pain, stiffness and function), responder status, and global impression of change.

Results: Pts (228) were randomized and treated (FX006 10 mg, n=58, FX006 40 mg, n=59, FX006 60 mg, n=60; TCA IR, n=51). Treatment arms were well balanced across demographic and baseline characteristics (mean baseline ADP: 6.5). FX006 40 mg was superior to TCA IR on weekly mean of ADP at Wk 5 to Wk 10 ($p<0.05$) (average pain reduction -0.9) (Figure 1). The 40 mg dose also demonstrated significant improvement over TCA IR ($p<0.05$) in secondary outcomes at Wk 8 (Table 1). Time to onset of pain relief was the same for FX006 40 mg and TCA IR. The 10 mg dose produced effects that were consistently improved relative to TCA IR but of lesser magnitude than those of the 40 mg dose. The 60 mg dose did not produce an improvement relative to the 40 mg dose. There were no related SAEs. AEs were generally mild and unrelated to study drug. Local knee-related AEs, lab assessments, ECGs and vital signs were unremarkable and similar across all treatments. Plasma PK across the FX006 doses were linear and dose-dependent. Peak plasma concentrations achieved with TCA IR were 10X of that seen with FX006 40 mg.

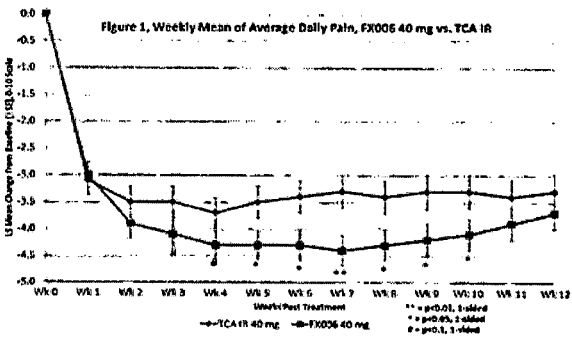


Table 1. Secondary efficacy endpoints at Week 8 comparing FX006 40 mg vs. TCA IR 40 mg

	FX006 40 mg (n=59)	TCA IR 40 mg (n=51)
WOMAC A (pain) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.33 (0.098)	-0.96 (0.108)
LSMD vs TCA IR (90% CI)	-0.37 (-0.61, -0.13)	
1 sided p-value	0.0058	
WOMAC A1 (pain on walking) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.2 (0.12)	-0.8 (0.13)
LSMD vs TCA IR (90% CI)	-0.4 (-0.7, -0.1)	
1 sided p-value	0.0098	
WOMAC B (stiffness) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.49 (0.112)	-0.99 (0.124)
LSMD vs TCA IR (90% CI)	-0.49 (-0.77, -0.22)	
1 sided p-value	0.0018	
WOMAC C (function) (0-4 Likert scale)		
LSM change from baseline (SE)	-1.31 (0.096)	-0.94 (0.106)
LSMD vs TCA IR (90% CI)	-0.37 (-0.61, -0.14)	
1 sided p-value	0.0049	
OMERACT-OARSI ^a		
n (%)	53 (89.8%)	32 (69.6%)
p-value	0.0118	
OR (90% CI)	3.9 (1.6, 9.3)	
Responder >30% Improvement ^b		
n (%)	47 (85.5%)	27 (62.8%)
p-value	0.0119	
OR (90% CI)	3.5 (1.5, 7.9)	
PGIC (1-7 Likert scale)		
LSM change from baseline (SE)	1.8 (0.16)	2.6 (0.17)
LSMD vs TCA IR (90% CI)	-0.7 (-1.1, -0.3)	
1 sided p-value	0.0013	
CGIC (1-7 Likert scale)		
LSM change from baseline (SE)	1.8 (0.16)	2.6 (0.17)
LSMD vs TCA IR (90% CI)	-0.7 (-1.1, -0.3)	
1 sided p-value	0.0013	

a n=59 for FX006 40 mg; n=46 for TCA IR
b n=55 for FX006 40 mg; n=43 for TCA IR
LSM = least squares mean; LSMD = least square means difference; WOMAC = Western Ontario and McMaster Osteoarthritis Index; OMERACT-OARSI = Outcome Measures in Rheumatoid Arthritis Clinical Trials- Osteoarthritis Research Society International; PGIC = Patient Global Impression of Change; CGIC = Clinical Global Impression of Change

Conclusion: In pts with OA of the knee, the 40 mg dose of FX006 demonstrated an amplified and prolonged therapeutic effect relative to TCA IR. A Phase 3 study of the 40 mg dose of FX006 is being planned.

Disclosure: N. Bodick, Flexion Therapeutics, 1, Flexion Therapeutics, 3; J. Lufkin, Flexion Therapeutics, 1, Flexion Therapeutics, 3; C. Willwerth, Flexion Therapeutics, 1, Flexion Therapeutics, 3; P. Lachance, None; G. Jassey, None; A. Gupta, None; A. Chris, None; M. Russo, None; M. O'Mahony, None; S. Hencin, None; L. Murdoch, None; F. de Looze, None; D. Hunter, None; M. Clayman, Flexion Therapeutics, 1, Flexion Therapeutics, 3.

Osteoarthritis and Cartilage



Sustained efficacy of a single intra-articular dose of FX006 in a rat model of repeated localized knee arthritis



A. Kumar [†]*, A.M. Bendele [‡], R.C. Blanks [§], N. Bodick [†]

[†] Flexion Therapeutics, Inc., Burlington, MA, USA

[‡] Bolder BioPATH, Inc., Boulder, CO, USA

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SUMMARY

Objective: To evaluate the efficacy of a single intra-articular (IA) dose of FX006, an extended-release formulation of triamcinolone acetonide (TCA) in poly(lactic-co-glycolic acid) (PLGA) microspheres, on the sequelae of repeated episodes of synovitis.

Design: Three flares of localized synovitis in the right knee of rats were induced over 4 weeks following a single IA injection of various doses of FX006, Kenalog[®] (TCA immediate release or TCA IR), or vehicle. Gait scores were employed to assess analgesic effect, and the joints were evaluated by histology at the end of the study. TCA plasma concentrations and corticosterone levels were monitored through the study.

Results: A single IA dose of 0.28 mg FX006 significantly improved gait scores through all three reactivations. TCA IR at 0.06 mg (providing comparable plasma TCA exposure, 10-fold higher C_{max}) demonstrated comparable benefit through the first reactivation only and reduced-to-no efficacy thereafter. Significantly improved histological joint scores were observed with effective doses of FX006 but not with TCA IR. Corticosterone levels were initially decreased following both TCA IR and FX006 treatment, but recovered by Day 14.

Conclusions: In localized, repeated synovitis in rats, sustained release of TCA following a single IA injection of FX006 significantly prolonged analgesia relative to TCA IR and significantly improved histological scores with no adverse effect on the HPA axis. Since synovitis can contribute to the pathophysiology of multiple joint diseases such as osteoarthritis (OA), RA and gout, FX006 may be an important treatment option for these conditions.

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Introduction

Synovial inflammation contributes to the underlying pathology of a number of disease states including gouty arthritis, psoriatic arthritis, rheumatoid arthritis, and juvenile rheumatoid arthritis. While osteoarthritis (OA) has historically been considered a non-inflammatory condition, recent literature suggests that synovitis is present in all stages of knee OA^{1–3} and correlates to both the occurrence of symptoms^{4–8} and structural progression^{9–14}. In OA, available evidence suggests that synovial inflammation produces

proinflammatory cytokines such as IL-1 and TNF- α that may reduce secretion of lubricin^{15,16} and mediate cartilage damage through activation of metalloproteinases^{17–22}.

Intra-articular (IA) administration of immediate release (suspension) corticosteroids, including triamcinolone acetonide (TCA), has been routine in the management of knee OA for decades. However, in well-controlled studies, IA corticosteroids demonstrate a duration of effect of only 1–3 weeks^{23–25}. FX006 has been developed to extend the duration of effect of TCA in patients with OA of the knee. FX006 is formulated for IA injection and contains TCA, USP, formulated in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (w/w).

Poly(lactide-co-glycolic acid) is a biodegradable co-polymer of poly-lactide and poly-glycolide that *in vivo* is gradually degraded to carbon dioxide and water. It is widely regarded as biocompatible and several injectable sustained-release microsphere and other implantable PLGA drug products and devices have been approved for commercial use²⁶. The prolonged release of TCA from PLGA

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^a Current affiliation.

following IA injection of FX006 is expected to both sustain local anti-inflammatory effects relative to TCA IR, and avoid the high peak plasma TCA concentrations associated with TCA IR. The objective of the current study was to test this hypothesis in a rat model of localized, repeated synovitis which contributes to several joint diseases including many patients with OA.

Methods

FX006

FX006 contains TCA, USP, formulated in 75:25 poly(lactic-co-glycolic acid) (PLGA) microspheres with a nominal drug load of 25% (w/w) and is provided as a sterile white-to-off-white powder for reconstitution. The drug product is reconstituted with diluent containing an isotonic, sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), carboxymethylcellulose sodium (CMC; 0.5% w/w) and polysorbate-80 (0.1% w/w) to form a suspension prior to IA injection. The microspheres range in size from 20 to 100 µm (median = 42 µm).

Animal model development

A new OA-like model was developed in rats wherein localized monoarticular arthritis/synovitis was induced in the right knee of Male Lewis rats^{27,28}. Following a priming IA injection of streptococcal cell wall peptidoglycan polysaccharide (PGPS; 100P fraction with 5–8 mg rhamnose/mL from Lee Laboratories) repeated episodes of synovitis in the right knee were induced by administering PGPS intravenously.

Male Lewis rats weighing 242–265 g at initial randomization by body weight (Day –18) were obtained from Charles River Laboratories, Inc., Wilmington, MA and housed 5 to a cage. The study design was approved by Bolder BioPATH's Institutional Animal Care and Use Committee (IACUC), Boulder, CO. Animals were acclimated for 10 days prior to being placed on study. An attending veterinarian was on site or on call during the live phase of the study. No concurrent medications were given. Housing of the animals throughout the study conformed to the guidelines cited in the Guide for the Care and Use of Laboratory Animals and the applicable standard operating procedures of Bolder BioPATH, Inc.

A timeline of study procedures is presented in Fig. 1. On Day –18, following anesthesia with 3% isoflurane, the right knees of rats were sensitized/primed by IA injection of PGPS (50 µL of 0.125 mg/mL). The day after IA sensitization, animals with no knee discomfort were eliminated from the test article groups and placed into the baseline group. Baseline assessments were performed on Day –3 and animals were re-randomized based on the

degree of pain/swelling (assessed as below) to ensure similar weight-bearing deficiency across treatment groups. On Day 0 (two+ weeks following sensitization) when the acute phase of inflammation had passed, a tail vein injection of PGPS (0.5 mL of 0.4 mg/mL) was administered to reactivate knee inflammation and local right knee pain. Flares were similarly induced again on Days 14 and 28. In this manner, synovitis/arthritis was kept localized to the right knee in rats. Ankle swelling was monitored using calipers in the animals to check for spreading of the inflammatory response and loss of localization to the right knee. It was possible to keep synovitis/arthritis localized for three reactivation episodes, 2 weeks apart for a total duration of just over a month (32 days). TCA IR (Kenalog-40®) was purchased from Bristol-Myers Squibb. FX006 (25% TCA in 75:25 PLGA microspheres) was provided by Flexion Therapeutics as a powder that was refrigerated until reconstitution in diluent (sterile aqueous solution of sodium chloride (NaCl; 0.9% w/w), sodium carboxymethylcellulose (NaCMC 0.5% w/w) and polysorbate-80 (0.1% w/w)). Diluent, FX006 or TCA IR was administered in the index knee by a single IA injection 2.5 h prior to the first reactivation of arthritis/synovitis by PGPS on Day 0 (n = 10/group; 2 cages/group based on pilot studies performed earlier). Differences in weight-bearing and gait (as a measure of joint pain experienced by the animals), plasma pharmacokinetics and pharmacodynamics (hypothalamus-pituitary-adrenal (HPA) axis effect) of TCA were characterized to compare the efficacy of a single IA dose of FX006 with TCA IR. The duration of efficacy of single IA doses of FX006 or TCA IR, (each given only once before the first reactivation on Day 0) was assessed by scoring joint pain/impaired gait, before and 1, 2 and 4 days following each reactivation (flare of synovitis/arthritis) – reactivations performed on Days 0, 14 and 28; pain assessments on Days –3 (before first reactivation), 1, 2, 4, 14 (before second reactivation), 15, 16, 18, 28 (before third reactivation), 29, 30, 32. After that point, the arthritis observed in the animals become more wide-spread (monitored by ankle swelling) making the attribution of pain to the index knee more difficult. Hence, this protocol allowed for prolonged assessment of the efficacy of single IA doses of FX006 and TCA IR through Day 32 when the experiment was terminated and the knee joints were collected for evaluation by histopathology.

Dose selection

Pharmacokinetics and effects on HPA axis function (cortisol suppression) for a range of doses of FX006 and TCA IR were evaluated in a separate study of Male Lewis rats to assist in dose selection for the present study. Following IA administration of 0.28 mg of FX006 in that study, cortisol levels returned to baseline within 14 days of administration, a pattern of cortisol suppression

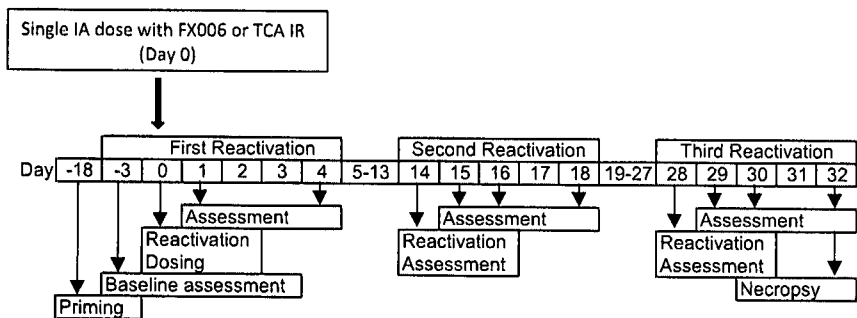


Fig. 1. The timeline of study procedures and assessments is shown in the schematic above and described in the text.

consistent with that observed in the clinic following administration of TCA IR²⁹ at doses that are considered effective and well tolerated. The doses of FX006 were selected to be 0.28, 0.12 or 0.03 mg TCA. Data from this study also suggested that TCA IR at a dose of 0.06 mg would provide overall systemic TCA exposure comparable to that of FX006 at a dose of 0.28 mg (approximately 350 h ng/mL). This dose of TCA IR also produced approximately the same maximum plasma TCA concentration as the labeled dose of 40 mg IA injection of TCA IR in humans (C_{max} ~12 ng/mL)²⁹. Initial dose-range finding experiments in the localized knee arthritis rat model also suggested that a dose of TCA IR of 0.06 mg would have a duration of efficacy of 1–3 weeks matching the duration of effect observed in clinical practice^{23–25}. The selected doses of TCA IR were 0.06 or 0.03 mg FX006, TCA IR or vehicle (diluent; control animals) were all administered as single IA injections in the sensitized right knee 2.5 h prior to the first reactivation of arthritis/synovitis by PGPS on Day 0.

Assessment of pain (Gait Scores)

Gait analysis was performed by applying black ink to the ventral surface of the rear feet of all rats and allowing them to walk the full length of a sheet of paper. Animals were observed visually and footprints made by the right injected leg were compared with the left uninjected one to assess weight bearing during movement. Gait was scored as shown in Table I.

HPA axis function (corticosterone levels)

Serum corticosterone levels were measured following morning blood collections via the tail vein in samples taken at baseline (Day -4), Day 0 (2 h post-dose with vehicle, FX006 or TCA IR, just prior to reactivation with PGPS), then Days 3, 14, 17, 28 and 31. A Mouse and Rat Corticosterone ELISA kit from Kamiya Biomedical Company was used in accordance with provided instructions with a 1:40 dilution.

Plasma pharmacokinetics

Blood samples in EDTA were collected at the same time points utilized for the corticosterone assay and placed on crushed wet ice until centrifugation. The resultant plasma was frozen immediately over dry ice. Plasma TCA levels were measured using a qualified bioanalytical LC-MS/MS assay. Non-compartmental pharmacokinetic analysis of concentration-time data was performed using WinNonlin Version 5.3.

Table I
Scoring scheme for gait in rats

Gait scores	Description/Criteria
0	Normal, equal ink staining on both feet
1	Slight limp, toe staining evident and some heel staining for all steps, no carrying or dragging. If left has very little heel staining (rat walks mainly on toes) then slightly (approximately 25%) less toe staining in right leg vs left for most steps
2	Limping, toes only staining for all steps, no carrying or dragging. If left has very little heel staining (rat walks mainly on toes) then approximately 50% less toe staining in right leg vs left for most steps
3	Dragging and carrying leg, black drag marks from dorsal side of foot present or some attempt to use right as evidenced by minimal toe staining in at least one print, may pause and place right foot down for a single step (or approximately 75% less staining on right vs left)
4	Carrying leg entire time, no staining from painful leg or only minor black drag marks, no toe staining in any print (100% less staining on right vs left)

Histopathology

Following 5–7 days in 5% formic acid decalcifier, rat knees were cut into two approximately equal halves and processed for paraffin embedding and then stained with toluidine blue (for glycosaminoglycans). Tissues were examined microscopically by a board certified veterinary pathologist (Dr Alison Bendele) and observations were entered into a computer-assisted data retrieval system. Scoring of knee sections was performed as shown in Table II.

Table II
Histological scoring scheme for knee joint sections

Grade scores	Description/Criteria
Bone resorption	
0	Normal
0.5	Score reserved for those that are normal on low magnification but have the earliest hint of small focal areas of resorption in a marginal zone
1	Minimal; small definite areas of resorption in marginal zones only
2	Mild; Small areas of resorption in marginal zones and extending up to 1/4 of the distance across the affected surface
3	Moderate; areas of resorption extend beyond marginal zones >1/4 but less than 1/2 of the subchondral surface
4	Marked; areas of resorption extend beyond marginal zones >1/2 but less than 3/4 of the subchondral surface
5	Severe; areas of resorption extend beyond marginal zones >3/4 of the subchondral surface
Inflammation	
0	Normal
0.5	Minimal generally focal infiltration of inflammatory cells in synovium
1	Minimal diffuse infiltration of inflammatory cells in synovium
2	Mild diffuse infiltration of inflammatory cells in synovium and extending into periarticular tissues
3	Moderate diffuse infiltration with moderate edema in synovium and extending into periarticular tissues
4	Marked diffuse infiltration with marked edema in synovium and extending into periarticular tissues
5	Severe diffuse infiltration with severe edema in synovium and extending into periarticular tissues
Pannus	
0	Normal
0.5	Minimal, focal or only few marginal zones affected
1	Minimal infiltration of pannus in cartilage and subchondral bone, primarily affects marginal zones
2	Mild infiltration (<1/4 of tibia or tarsals at marginal zones)
3	Moderate infiltration (1/4–1/3 of tibia or small tarsals affected at marginal zones)
4	Marked infiltration (1/2–3/4 of tibia or tarsals affected at marginal zones)
5	Severe infiltration (>3/4 of tibia or tarsals affected at marginal zones, severe distortion of overall architecture)
Cartilage damage	
0	Normal
0.5	Minimal, focal or only few marginal zones affected
1	Minimal; minimal to mild loss of toluidine blue staining with no obvious chondrocyte loss or collagen disruption, lesions mainly in marginal zones
2	Mild; mild loss of toluidine blue staining with focal mild (superficial) chondrocyte loss and/or collagen disruption mainly in marginal zones, may have 1–2 small areas of more severe degeneration
3	Moderate; moderate loss of toluidine blue staining with multifocal moderate (depth to middle zone) chondrocyte loss and/or collagen disruption on at least one surface but still mainly in marginal zones, may have 1–2 small areas of more severe degeneration
4	Marked; marked loss of toluidine blue staining with multifocal marked (depth to deep zone or tidemark) chondrocyte loss and/or collagen disruption on at least one surface
5	Severe; severe diffuse loss of toluidine blue staining with multifocal severe (depth to tidemark) chondrocyte loss and/or collagen disruption affecting more than two cartilage surfaces

Statistical analysis

Data were analyzed using a one-way analysis of variance (necropsy data such as organ weights and certain in-life measurements such as ankle diameters) with a Dunnett's multiple comparison. Gait and histopathology scores were evaluated using a Kruskal–Wallis test (non-parametric) with appropriate Dunn's multiple comparison post-test. ELISA data were evaluated by the Student's *t*-test. Significance for all tests was set at $P \leq 0.05$.

Results

Assessment of pain/gait impairment

Upon the first reactivation of arthritis, vehicle-treated control animals demonstrated painful gait as demonstrated by high (abnormal) scores (3.5 out of a maximum of 4) [Fig. 2(A) and (B)]. FX006 at 0.28 mg had good analgesic efficacy as demonstrated by near-normal gait scores on Days 1, 2 and 4 following the first reactivation [Fig. 2(A) and (B)]. After that, the animals accommodated to the pain and the transient flare of synovitis resolved. Further assessments of efficacy were similarly performed 1–4 days after the two subsequent reactivations. The 0.28 mg dose of FX006 continued to be efficacious following the second and third reactivations on Days 15–18 and Days 29–32 by which time the HPA axis function was normal [see accompanying corticosterone levels Fig. 4(A)]. Animals injected with 0.06 mg of TCA IR on Day 0 (which produces initial plasma concentrations approximately 10-fold that observed with the 0.28 mg dose of FX006 and comparable overall systemic TCA exposure) demonstrated significant improvement in gait scores through the first reactivation, diminution of effect after the second reactivation and absence of effect following the third reactivation [Fig. 2(A) and (B)]. There were 10 rats/group at the start. Gait data were excluded for animals that showed ankle swelling – one animal in most groups at second reactivation and 1–7 animals across groups at third activation leading to study termination at this point.

Overall, a clear dose-dependent analgesic response was noted for both FX006 and TCA IR [Fig. 2(A)]. Further, the duration of efficacy of TCA (single doses of either FX006 or TCA IR given before the first reactivation of arthritis) appeared to be a function of dose; however, the prolonged release of TCA from the PLGA microspheres in FX006 resulted in more sustained efficacy than TCA IR.

Assessment of plasma concentrations of TCA

Plasma TCA concentration-time curves for all treatment groups ($n = 5$ /group/time point) are shown in Fig. 3. IA FX006 provides a slow, sustained and smooth TCA release, eliminating the early spike in plasma concentration observed with TCA IR suspension. A limited non-compartmental plasma pharmacokinetic analysis was performed with these concentration data from the relatively small number of time points that were samples from the study animals. Mean peak plasma concentrations with FX006 at 0.28 mg were about 10-fold lower than those achieved with TCA IR at 0.06 mg ($C_{\max}$ 1.68 vs 17.3 ng/mL; $P \leq 0.05$). The corresponding overall systemic TCA exposure at these doses was comparable ($AUC_{0-\infty}$ 587 vs 324 h ng/mL).

Assessment of HPA axis effect of TCA

Corticosterone measurements in the study animals (as an indicator of HPA axis function) were measured as change from baseline for each treatment group at several time points ($n = 5$ /group/time point) through the study [Fig. 4(A)]. In general the corticosterone

data in this study were more variable than were observed in the separate study in normal healthy unmanipulated animals. The increased variability is likely due to the pain and stress resultant for the induced synovitis and study-related handling procedures. As shown in Fig. 4(A), all treatment groups had similar corticosterone levels at baseline, all were initially somewhat inhibited and all groups recovered by Day 14. A PK-PD analysis demonstrated that consistent with previously reported investigations in humans³⁰, inhibition of corticosterone was correlated with systemic TCA levels (for both FX006 and TCA IR) in rats and followed a classical inhibitory model as shown in Fig. 4(B) below. The IC_{50} in rats was about 1 ng/mL which is also consistent with a previous report in humans²⁹. FX006 achieved prolonged analgesic efficacy with a $C_{\max}$ of only 1.68 ng/mL at 0.28 mg (highest dose) and with no prolonged inhibition of HPA axis function.

Assessment of joint structure

Histopathological evaluation of the index knees ($n = 2$ –7/group) taken from vehicle-treated rats at the end of the study (Day 32; 4 days following the third and final reactivation of synovitis) showed marked-to-severe inflammation with minimal-to-moderate pannus formation and cartilage damage, and mild bone resorption [Fig. 5(A) and (B)]. The mean summed histopathology score (a composite of the four individual parameters: inflammation, pannus, cartilage damage, bone resorption) was 11 out of a possible 20. At the high and mid dose (0.28 and 0.12 mg) FX006 demonstrated a statistically significant improvement in the composite histological score and each component score relative to disease controls as shown in Fig. 5(A) and (B). The extended duration of analgesic and presumably anti-inflammatory efficacy with FX006 resulted in a significant improvement in histological scores of joint tissues with scores approximating normal tissue architecture at the high and mid dose of FX006.

On the other hand, the 0.06 mg and the 0.03 mg doses of TCA IR were associated with a smaller, non-significant improvement in histological scores as compared to diseased controls. It is noted that the lowest dose of FX006, which was not as effective as the two higher doses in this rat model, had a similar small, non-significant effect on histological score.

Representative photomicrographs of knee sections for a vehicle control/diseased rat and rats treated with the highest doses of TCA IR or FX006 at the end of the study following the third reactivation of synovitis on Day 32 are shown in Fig. 6. Infiltration of inflammatory cells into the synovium, cartilage damage and bone resorption were noted in the vehicle control animals (A). These were also noted following TCA IR treatment (B) however, treatment with a single IA dose of FX006 which achieved sustained analgesic efficacy also resulted in prevention of damage to the joint and especially also to the cartilage such that these rats had near-normal joints over the course of this study despite the induction and three cycles of reactivation of synovitis (C).

Discussion

Synovitis contributes to the underlying pathology and joint degeneration in a number of disease states such as rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, gouty arthritis and OA. In OA, now described as a disease of the "whole joint", inflammatory mediators can be released from both synoviocytes and chondrocytes³¹ and dysregulation of complement has also been demonstrated³². Suppression of synovial inflammation, cytokine production and metalloproteinase synthesis with IA corticosteroids has the potential to reduce structural damage and limit disease progression in inflammatory joint diseases including OA in

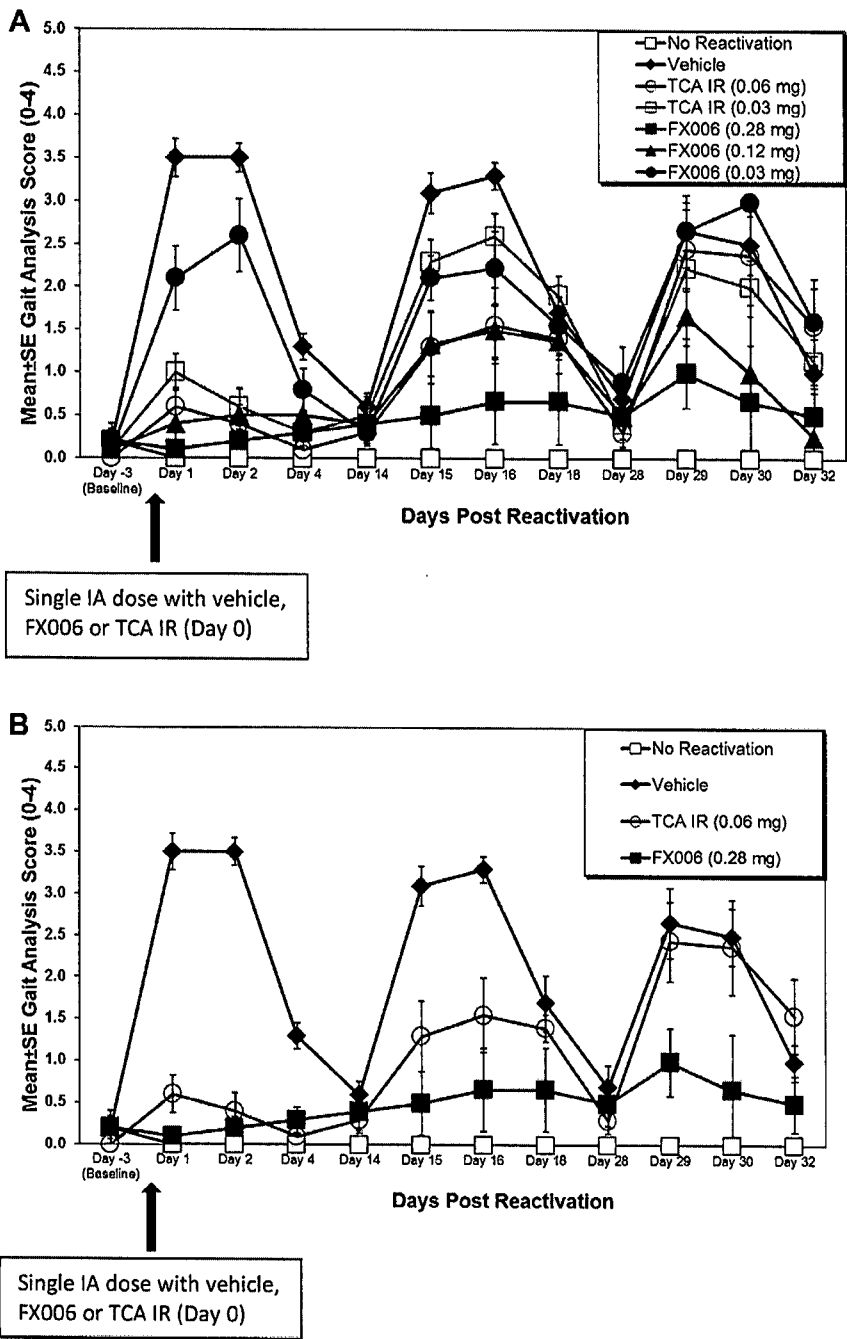


Fig. 2. Gait analysis scores (mean $\pm$ S.E.M.) are shown for control rats (black diamonds) and for rats treated with FX006 or TCA IR through three reactivations of localized synovitis/arthritis (A) All treatment groups (B) Control animals and groups treated with the highest doses of FX006 (red squares) and TCA IR (purple open circles) that provide comparable systemic exposure to TCA. A single IA injection of FX006 on Day 0, most notably at 0.28 mg, resulted in sustained analgesic efficacy throughout the study period achieving statistical significance compared to vehicle control on Days 1, 2, 4, 15 and 16 ($P \leq 0.05$ Kruskal–Wallis test with Dunn's multiple comparison post-test).

humans^{33,34}. It follows that sustained suppression of synovitis could not only provide prolonged pain relief and functional improvement, but also may limit structural progression in OA.

FX006 provides an extended and predictable release of TCA as the biocompatible PLGA microspheres slowly degrade. A single IA dose of FX006 results in less systemically bioavailable TCA when compared to a matched dose of TCA IR on account of slower release and absorption into the systemic circulation. By providing prolonged local exposure to TCA while minimizing systemic exposure,

IA injection of FX006 is expected to have sustained anti-inflammatory and analgesic efficacy with minimal adverse effects.

In the present study, a localized rat model of knee arthritis with synovitis was developed and validated using a dose of TCA IR that demonstrated the short-term efficacy of 1–3 weeks routinely observed in the clinic^{23–25}. This model allowed the evaluation of the efficacy of FX006, an extended-release IA formulation of TCA, and comparison with the efficacy profile of TCA IR. The results demonstrate a clear dose response for both TCA IR and FX006

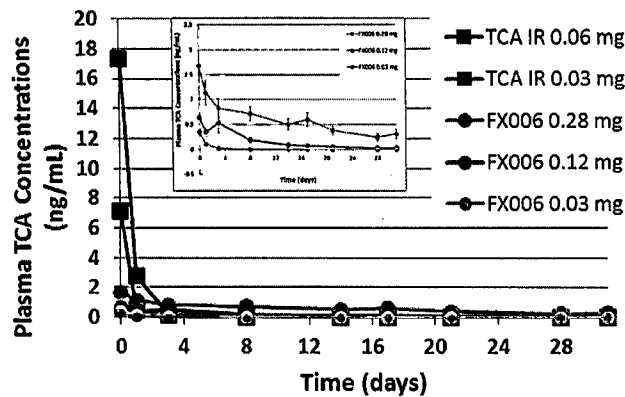


Fig. 3. Mean plasma concentrations of TCA over time measured in animals treated with FX006 or TCA IR are shown for all FX006 and TCA IR groups. Inset shows the low TCA concentrations (mean ± s.e.m.) in the FX006 groups on a smaller scale.

treatment in terms of both degree and duration of analgesic effects and anti-inflammatory efficacy. Further, FX006 at 0.28 mg prolonged pain relief relative to TCA IR administered at a dose that provided comparable systemic exposure to TCA. Histopathologic evaluation extended the results from gait and weight-bearing analyses, with significantly better near-normal knee joints in rats that received single doses of FX006 at 0.28 or 0.12 mg IA as compared to vehicle-treated controls that showed significant inflammation, pannus formation, cartilage damage and bone resorption. Low dose FX006 and TCA IR groups that did not have sustained anti-inflammatory/analgesic activity through the duration of the study (three reactivations of arthritis) also showed progression of the histological lesion/joint disease in this model.

Corticosteroid treatment has been demonstrated to have a protective effect on articular cartilage in models of *in vitro* structural/chemical damage^{35–37} and in animal models of inflammatory arthritis and OA^{38–42}. To provide a specific example, degenerative cartilage changes following IA injection of sodium iodoacetate (a chondrocyte metabolic inhibitor) include loss of staining with Safranin O (indicating loss of glycosaminoglycans) in cartilage, and depletion of chondrocytes; however, when triamcinolone

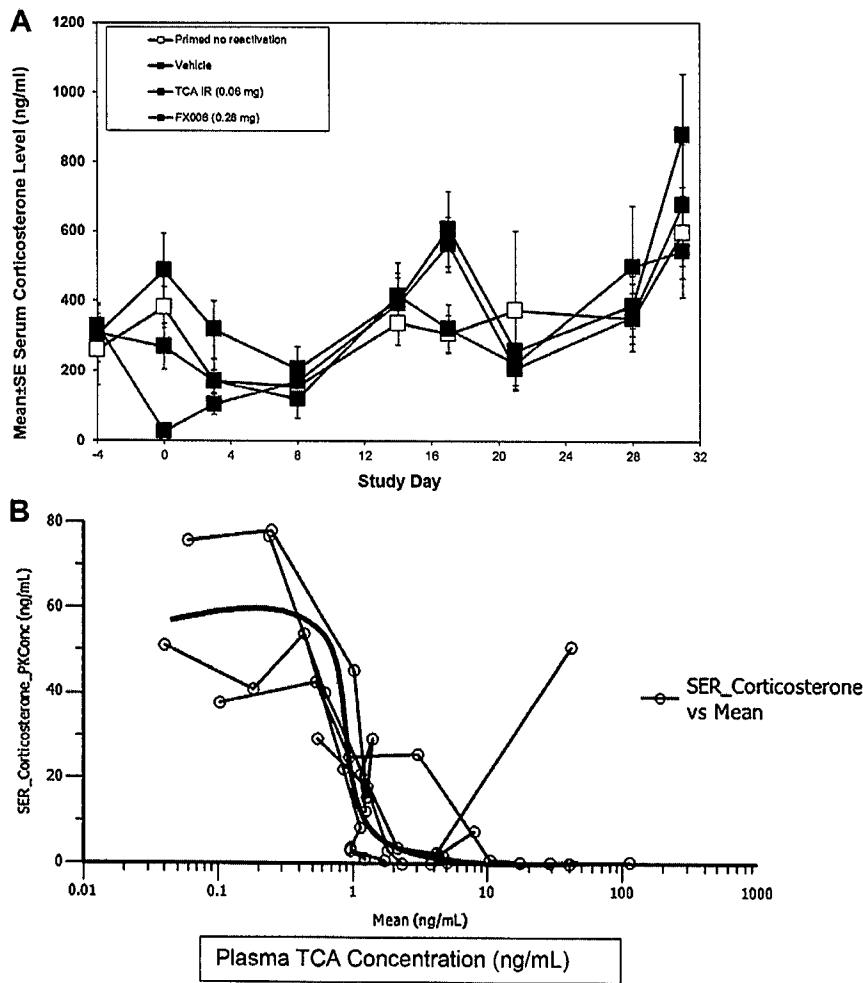


Fig. 4. (A) Serum corticosterone levels (mean ± s.e.m.) are shown over time for vehicle-treated rats and those animals treated with only the highest dose levels of FX006 or TCA IR for clarity since the data were variable in these animals, likely on account of the pain and stress experienced during the conduct of this study. The initial TCA-related inhibition immediately following dose administration, recovered in all animals by 2 weeks. (B) Serum corticosterone levels measured in FX006- or TCA IR-treated rats are shown as a function of plasma TCA concentration. This PK/PD analysis showed (red line) that HPA axis effects as measured by serum corticosterone were a function of systemic TCA concentration and serum corticosterone was inhibited when plasma concentration was above 1 ng/mL.

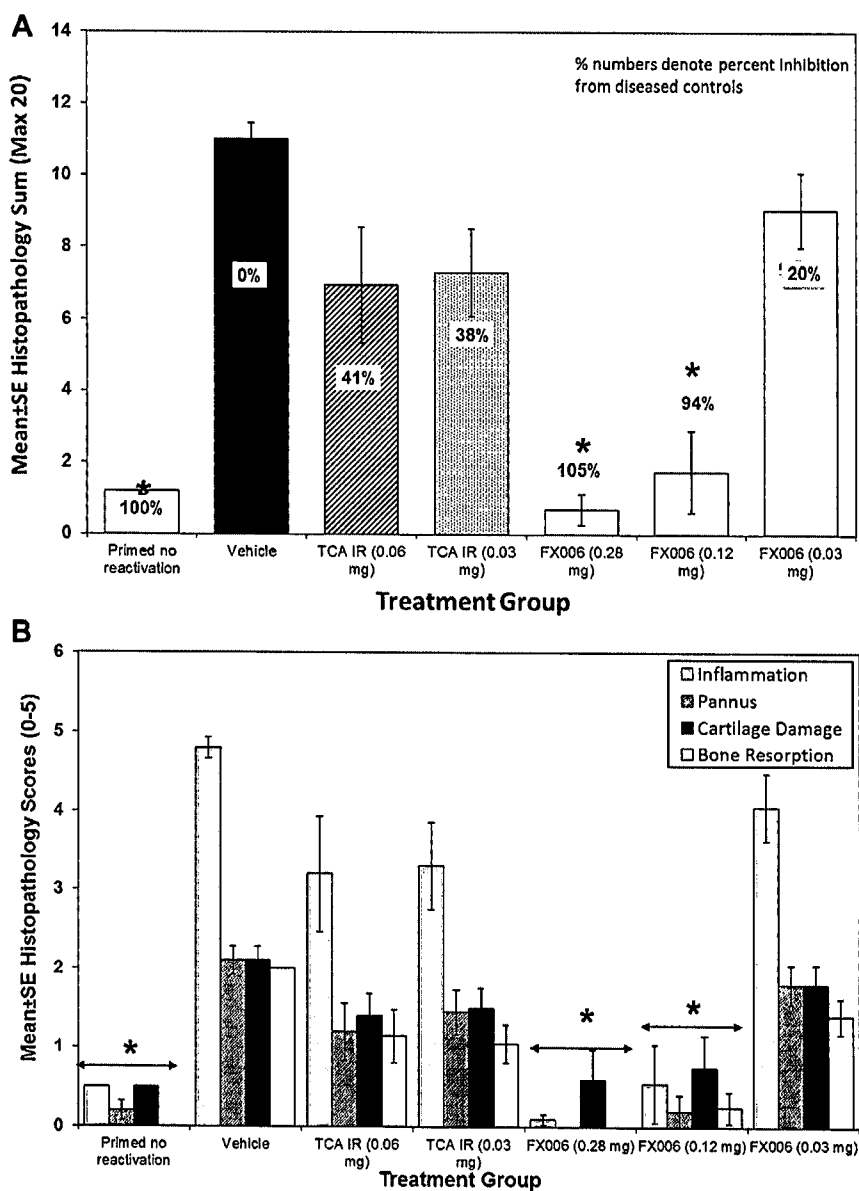


Fig. 5. Histopathological analysis (mean $\pm$ s.e.m.) of rat knee joints at the end of the study following the last of three reactivations of synovitis/arthritis demonstrated joint degeneration in vehicle-treated control animals. Treatment with a single IA injection of FX006 improved joint scores significantly ($P \leq 0.05$ Kruskal–Wallis test with Dunn's multiple comparison post-test at high- and mid-doses compared to vehicle control) as shown above in (A) Composite scores and (B) Individual scores for inflammation, cartilage damage, bone resorption and pannus formation. Treatment with TCA IR resulted in a smaller, non-significant improvement.

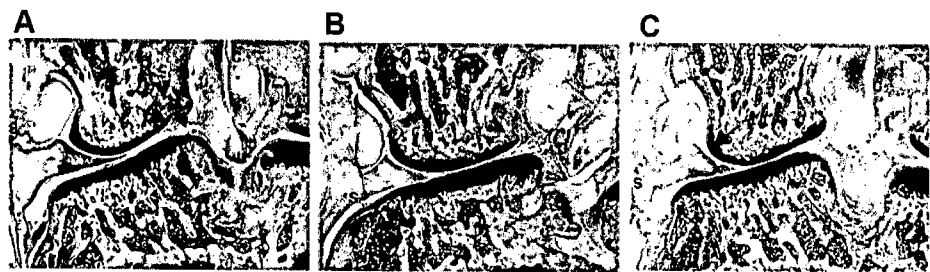


Fig. 6. These representative micrographs showing toluidine blue stained sections of knee joints taken from a (A) vehicle (B) TCA IR and (C) FX006 (0.28 mg)-treated rats. FX006-treatment resulted in joint preservation as can be noted in the near-normal joint architecture that was maintained following a single IA injection of 0.28 mg of FX006. Images taken at 25 $\times$; note cartilage (large arrow; damaged in the vehicle and TCA IR-treated rats and intact in the FX006-treated rat), pannus formation (small arrow; in vehicle animal only), bone resorption (arrowhead; in vehicle and TCA IR animals only). S = synovium (note severe inflammation in the vehicle and TCA IR-treated animals and normal synovium in the FX006-treated animal); C = cruciates/intracondylar connective tissue.

hexacetonide is injected into the knee 24 h after the IA injection of iodoacetate, pericellular staining with Safranin O persisted, and cell loss is less extensive⁴³. Consistent with these results, in the present study involving inflamed rat joints, FX006 conferred dose-dependent benefit to all joint structures assessed histologically that was greater than the benefit produced by TCA IR at a dose providing similar systemic exposure to TCA. In contrast to these and other data showing that corticosteroids reduce cartilage degradation in the context of joint inflammation, there is evidence in the literature that repeatedly injected corticosteroids have deleterious effect on cartilage in normal animal joints as well as in patients in clinical case reports^{44–46}. Most of these reports describe multiple, frequent IA steroid injections and none are controlled clinical studies. Given the protective effect on articular cartilage in models of inflammatory arthritis and OA, the relevance of these findings to the treatment of patients with OA is unclear. In current clinical practice, corticosteroid injections in the knee of patients with OA are administered approximately 3 million times per year in the US (IMS PharMetrics Plus database) and are generally well tolerated⁴⁷. Further, in a randomized, double-blind, clinical study in OA patients, IA injection of 40 mg TCA IR every 3 months for 2 years had no deleterious effect on knee structure vs saline injections as assessed by radiographic progression of joint space narrowing⁴⁸.

Finally, no adverse effect on the HPA axis was noted following IA treatment with FX006. Corticosterone levels in all TCA groups were significantly reduced relative to the vehicle controls shortly after dosing; however, by day 14, all groups recovered to baseline levels. Therefore despite prolonged local exposure to TCA with FX006, systemic concentrations remained low and these therapeutic doses of FX006 were very well tolerated.

It has been separately demonstrated that relative to TCA IR, the slow release and absorption of TCA from FX006 produces significantly lower systemic exposures to TCA. In multiple studies in rats and dogs, and even in human OA patients⁴⁹ it has been noted that at matched doses, $AUC_{0-\infty}$ for TCA is about half that with IA FX006 than with TCA IR. Further, AUC_{0-24} and C_{max} for TCA have been observed to be 10–30× lower with FX006 than with TCA IR at matched doses. In the present study, fewer samples were taken to minimize stress in these diseased animals but the trends in the PK parameters from a limited non-compartmental analysis were consistent with previous studies. At comparable exposures, C_{max} for FX006 at 0.28 mg was 1/10 that for TCA IR at 0.06 mg. Despite the lower absolute dose, the C_{max} in TCA IR-treated animals of 17 ng/mL was also greater than that reported following the labeled 40 mg IA dose of Kenalog® in patients²⁹.

In conclusion, the prolonged residence of TCA in the joint following a single IA dose of FX006 resulted in prolongation of analgesic effect in this rat model of localized, repeated knee synovitis/arthritis with a significant histological improvement in inflammation, pannus formation, cartilage damage and bone resorption. FX006 had these effects with low systemic exposure to TCA and without prolonged inhibition of the HPA axis function. Therefore in patients, especially those sub-groups in whom synovitis/inflammation is a major feature, the effect of FX006 can be expected to be greater and more durable than that of TCA IR in terms of pain relief as well as joint disease progression, particularly in the early stages of disease. Importantly, these data with FX006 demonstrate that TCA had no deleterious effect on cartilage as has been described in other settings, and consistent with other data in the literature, it actually reduced cartilage damage in this inflammatory milieu by slowing, arresting or reversing loss of articular cartilage.

This model was specifically developed to induce localized, repeated synovitis/arthritis in knees of rats that would allow assessment of the efficacy of a single IA injection of an extended-

release formulation of TCA. Further, the model was validated by employing a dose of TCA IR that demonstrates short-term efficacy similar to what is routinely noted in the clinic. Since only three reactivations of arthritis/synovitis at 2-week intervals were possible before the disease became more wide-spread, the available period of assessment was limited to 32 days. Animals demonstrating ankle swelling following the second reactivation were excluded from the third reactivation. Further, blood sampling for plasma TCA measurement was limited to only a few time points in these animals that were already undergoing numerous study-related procedures. Therefore the PK parameters calculated from these concentration-time data are more imprecise estimates as compared to more detailed PK assessments that have been separately performed for both FX006 and TCA IR. The pain and stress of arthritis in these animals also resulted in more variable corticosterone measurements as compared to separate studies in healthy animals. Nonetheless, the objectives of this study were met and the observations of efficacy of FX006 in ameliorating pain and improving joint structure were consistent and reliable.

The efficacy and safety of IA TCA IR has been established in the clinic for decades. FX006 has the potential to provide superior pain relief to TCA IR, and in two Phase II studies in patients with OA of the knee, FX006 has demonstrated local pharmacokinetics consistent with prolonged TCA residence in the joint and a prolonged and amplified analgesic effect, relative to a matched dose of TCA IR^{49,50}. In humans, the slow release of TCA from PLGA microspheres is expected to provide about 3 months of therapeutic TCA levels in the knee joint with lower systemic exposures to TCA than produced with 40 mg of IA Kenalog®-40, currently widely used in OA patients. FX006 has the potential not only provide prolonged pain relief and functional improvement, but also to limit disease progression without prolonged inhibition of the HPA axis function. FX006 may constitute a valuable treatment alternative in the expanding population of patients with OA.

Author contributions

All authors made substantial contributions to this work.

Anjali Kumar, PhD, FAHA – conception and design of the study, acquisition, analysis and interpretation of data, collection and assembly of data, drafting of the article and revising it critically, final approval of article.

Alison Bendele, DVM – conception and design of the study, acquisition, analysis and interpretation of data, revising article critically for important intellectual content, final approval of article.

Robert C Blanks, MS – conception and design of the study, synthesis of FX006, revising article critically for important intellectual content, final approval of article.

Neil Bodick, MD, PhD – conception and design of the study, revising article critically for important intellectual content, final approval of article.

Anjali Kumar, PhD, FAHA (akumar@flexiontherapeutics.com) takes responsibility for the integrity of this work as a whole, from inception to finished article.

Funding source and competing interest statement

Author Dr Neil Bodick is the co-founder and both he and Dr Anjali Kumar are employees of Flexion Therapeutics. Robert C Blanks was previously an employee of Flexion Therapeutics. Flexion Therapeutics is developing FX006 for treatment of pain in OA and sponsored the present study at Bolder BioPATH, a contract research organization. Dr Alison Bendele is the President and CEO of Bolder BioPATH and an occasional consultant to Flexion Therapeutics.

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INTELLECTUAL
PROPERTY
OFFICE

LETTERS PATENT

Number 607797

ELIZABETH THE SECOND, by the Grace of God Queen of New Zealand and Her Other Realms and Territories, Head of the Commonwealth, Defender of the Faith; To all to whom these presents shall come, Greeting:

WHEREAS pursuant to the Patents Act 1953 an application has been made for a patent of an invention for **CORTICOSTEROIDS FOR THE TREATMENT OF JOINT PAIN**

(more particularly described in the complete specification relating to the application)

AND WHEREAS

FLEXION THERAPEUTICS, INC., 300 Trade Center, Suite 2460, Woburn MA 01801, United States of America

(hereinafter together with his or their successors and assigns or any of them called "the patentee") is entitled to be registered as the proprietor of the patent hereinafter granted:

Address for service: **CULLENS, # 4817, PO Box 83000, Wellington 6440, New Zealand**

NOW, THEREFORE, We by these letters patent give and grant to the patentee our special licence, full power, sole privilege, and authority, that the patentee by himself, his agents, or licensees and no others, may subject to the provisions of any statute or regulation for the time being in force make, use, exercise and vend the said invention within New Zealand and its dependencies during a term of twenty years from 4 August 2011 and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the said term:

AND WE strictly command all our subjects whomsoever within New Zealand and its dependencies that they do not at any time during said term either directly or indirectly make use of or put into practice the said invention, nor in any way imitate the said invention without the consent, licence, or agreement of the patentee in writing under his hand, on pain of incurring such penalties as are prescribed by law and of being answerable to the patentee according to law for his damages thereby occasioned:

PROVIDED ALWAYS:

- (1) That these letters patent shall determine and become void if the patentee does not from time to time pay the renewal fees prescribed by law in respect of the patent:
- (2) That these letters patent are revocable on any of the grounds prescribed by the Patents Act 1953 as grounds for revoking letters patent:
- (3) That nothing in these letters patent shall prevent the granting of licences in the manner in which and for the considerations on which they may by law be granted:
- (4) That these letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these letters patent to be signed and sealed on 25 March 2015 with effect from 4 August 2011.



Mandy McDonald

Mandy McDonald
Commissioner of Patents, Trade Marks, and Designs



(12) **United States Patent**
Bodick et al.

(10) **Patent No.:** **US 8,828,440 B2**
(45) **Date of Patent:** **Sep. 9, 2014**

(54) **CORTICOSTEROIDS FOR THE TREATMENT OF JOINT PAIN**

(75) Inventors: **Neil Bodick**, Boston, MA (US); **Robert C. Blanks**, Auburndale, MA (US); **Anjali Kumar**, Belmont, MA (US); **Michael D. Clayman**, Gloucester, MA (US); **Mark Moran**, Orinda, CA (US)

(73) Assignee: **Flexion Therapeutics, Inc.**, Burlington, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/422,994**

(22) Filed: **Mar. 16, 2012**

(65) **Prior Publication Data**

US 2012/0288534 A1 Nov. 15, 2012

Related U.S. Application Data

(63) Continuation of application No. 13/198,168, filed on Aug. 4, 2011, now abandoned.

(60) Provisional application No. 61/370,666, filed on Aug. 4, 2010.

(51) **Int. Cl.**
A61K 9/14 (2006.01)
A61K 9/50 (2006.01)
A61K 31/56 (2006.01)
A61K 31/573 (2006.01)
A61K 9/00 (2006.01)
A61K 9/16 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 9/1647** (2013.01); **A61K 31/573** (2013.01); **A61K 9/0024** (2013.01); **A61K 9/0019** (2013.01); **A61K 9/1641** (2013.01); **A61K 9/1694** (2013.01)
USPC **424/489**; **424/497**; **514/181**

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — David J Blanchard

Assistant Examiner — Tigabu Kassa

(74) **Attorney, Agent, or Firm** — Cooley LLP

(57) **ABSTRACT**

Corticosteroid microparticle formulations are provided for use for treating pain, including pain caused by inflammatory diseases such as osteoarthritis or rheumatoid arthritis, and for slowing, arresting or reversing structural damage to tissues caused by an inflammatory disease, for example damage to articular and/or peri-articular tissues caused by osteoarthritis or rheumatoid arthritis. Corticosteroid microparticle formulations are administered locally as a sustained release dosage form (with or without an immediate release component) that results in efficacy accompanied by clinically insignificant or no measurable effect on endogenous cortisol production.

10 Claims, 30 Drawing Sheets

31
33

(56)

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FIG. 1

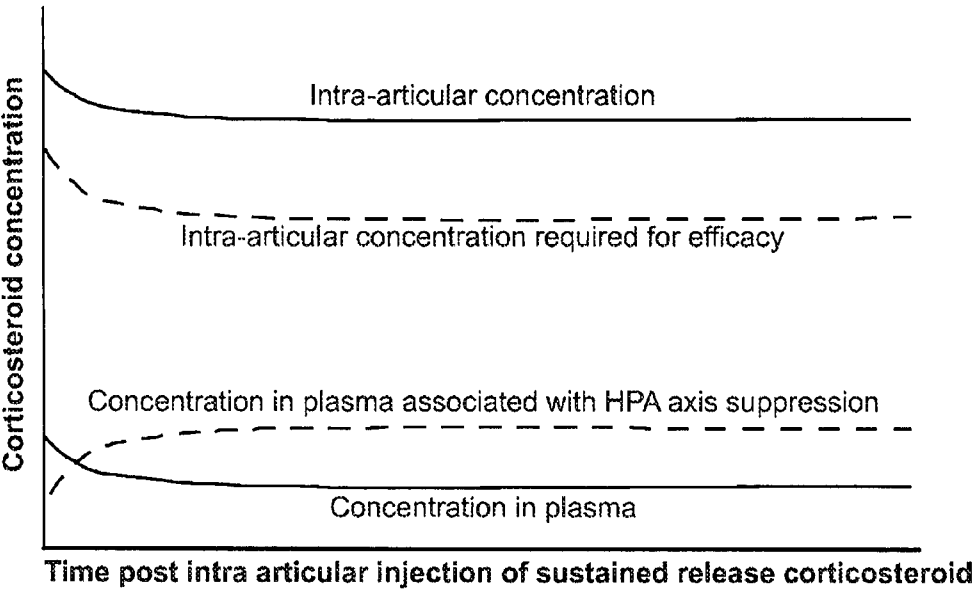
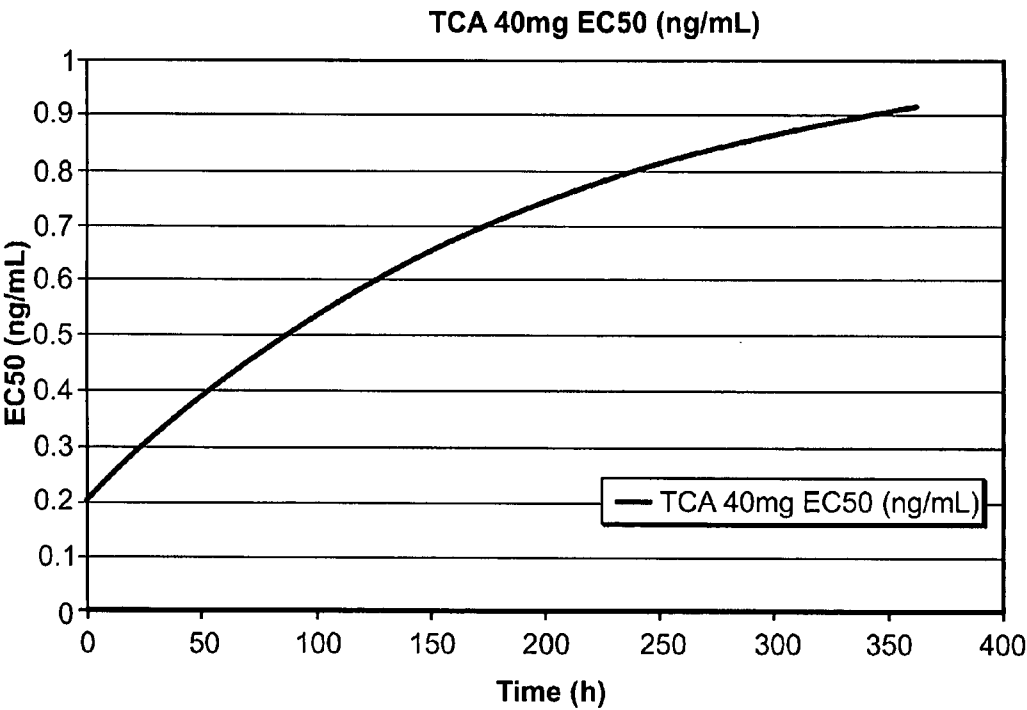


FIG. 2



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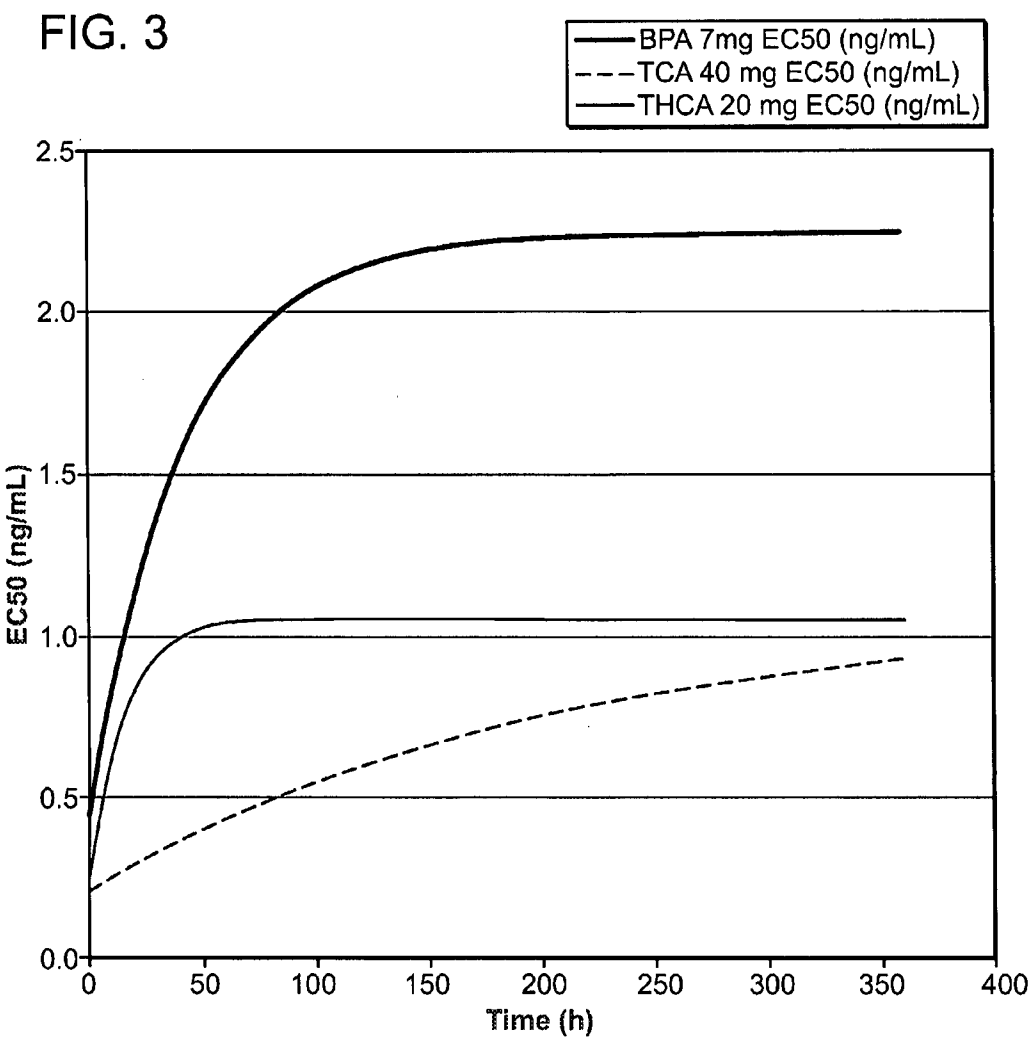
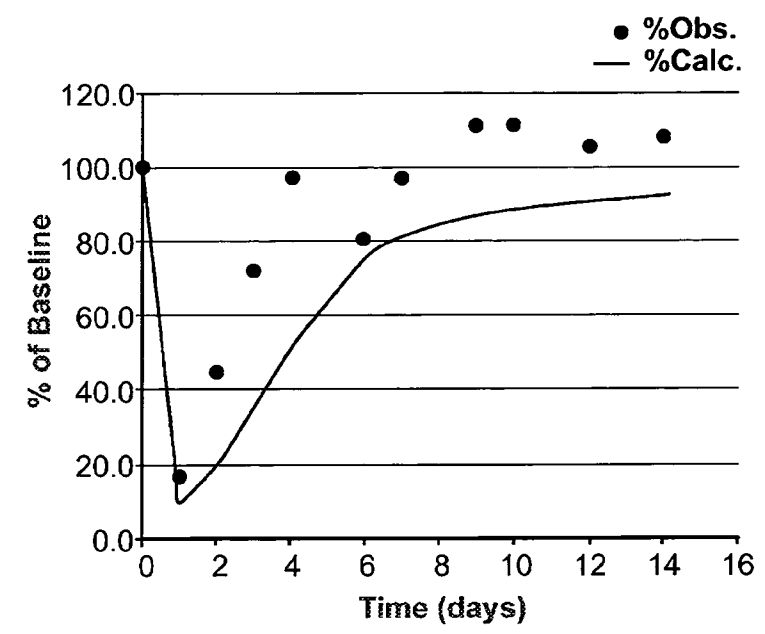
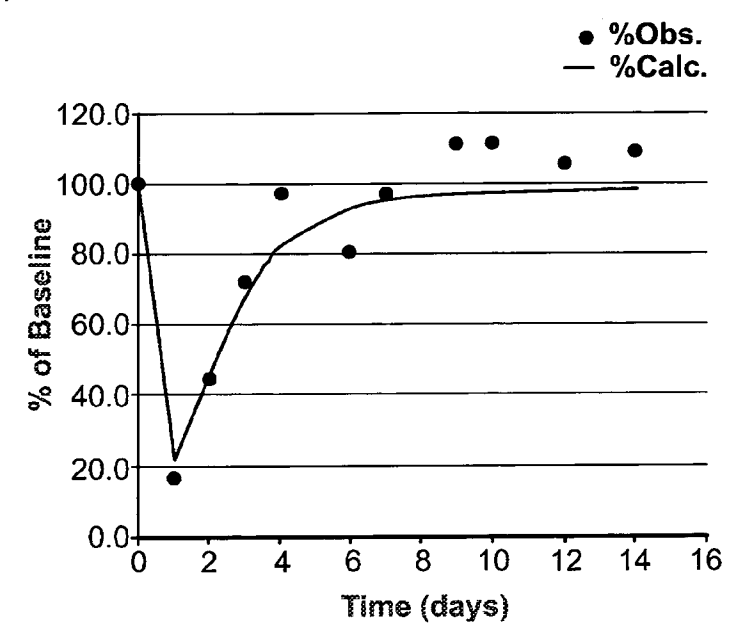


FIG. 4A



Observed vs. Predicted
Without Correction for a Change in Sensitivity
of the HPA Axis

BPA7



Observed vs. Predicted With
Correction for a Change in Sensitivity of
the HPA Axis

FIG. 4B

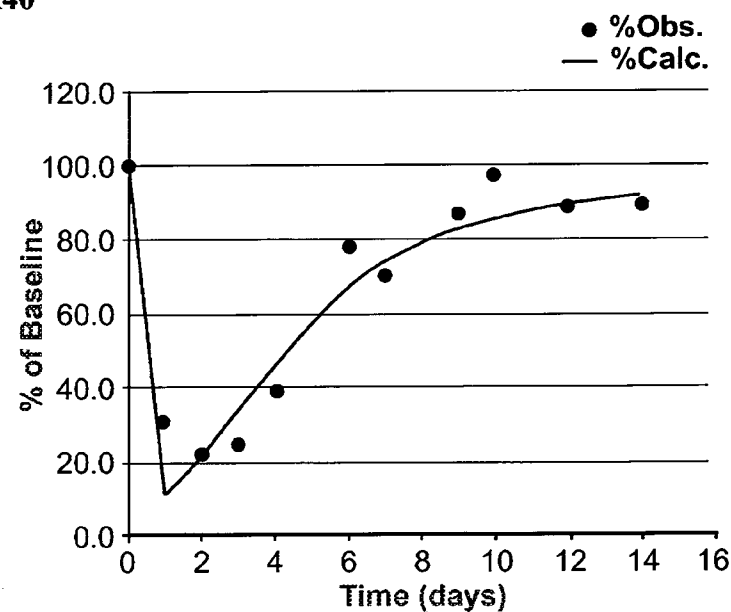
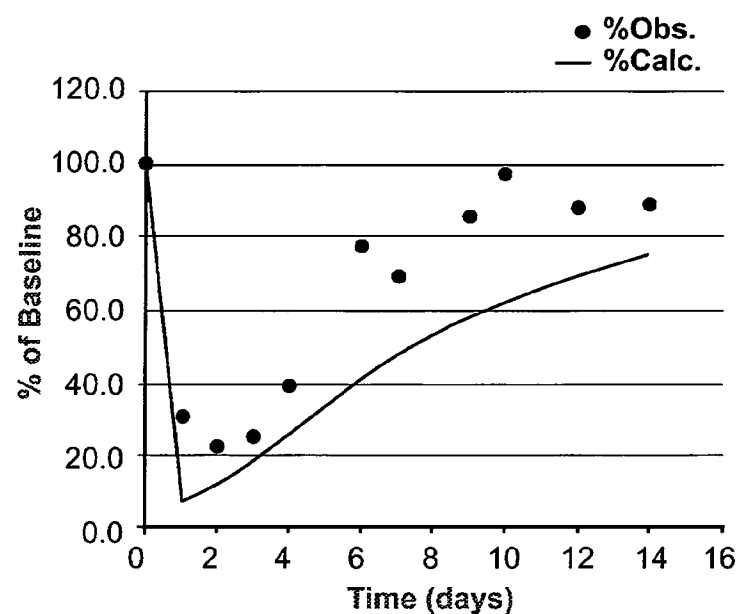
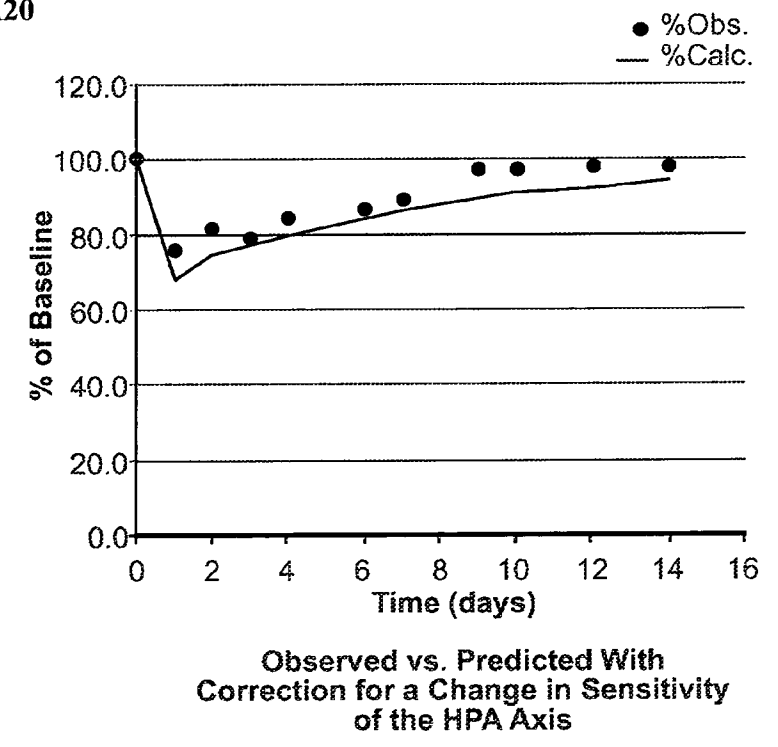
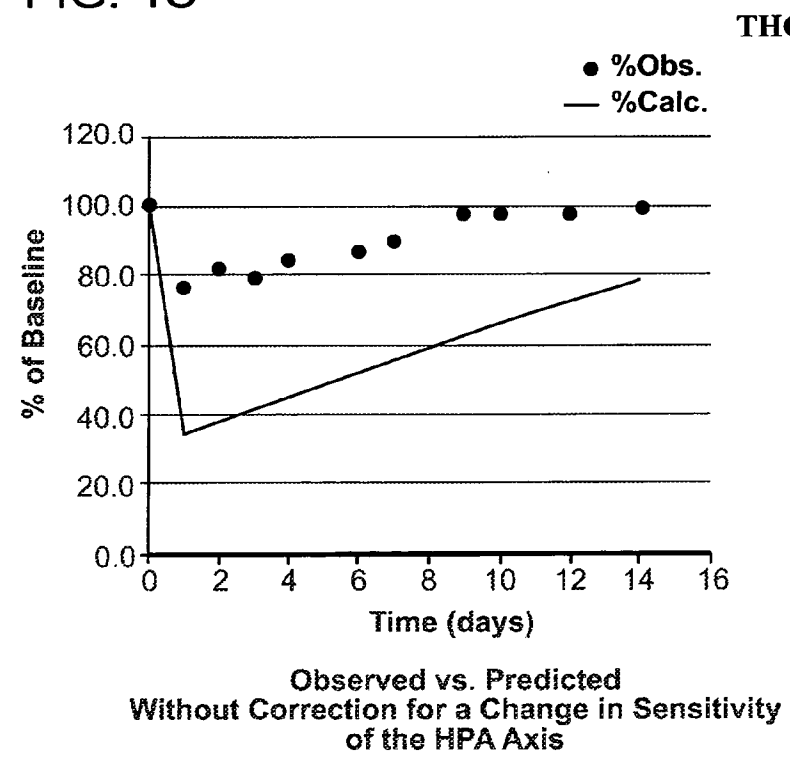


FIG. 4C



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FIG. 5

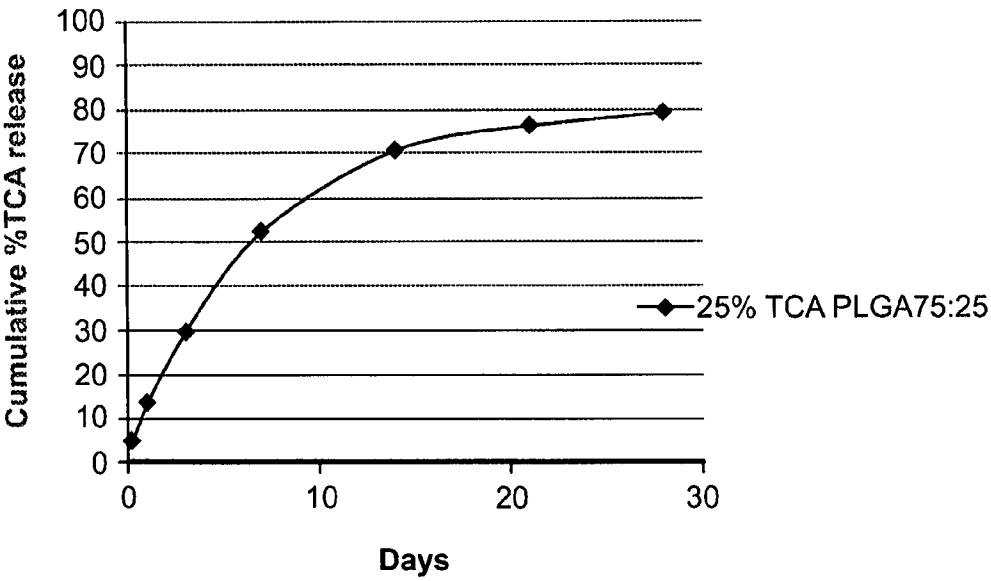
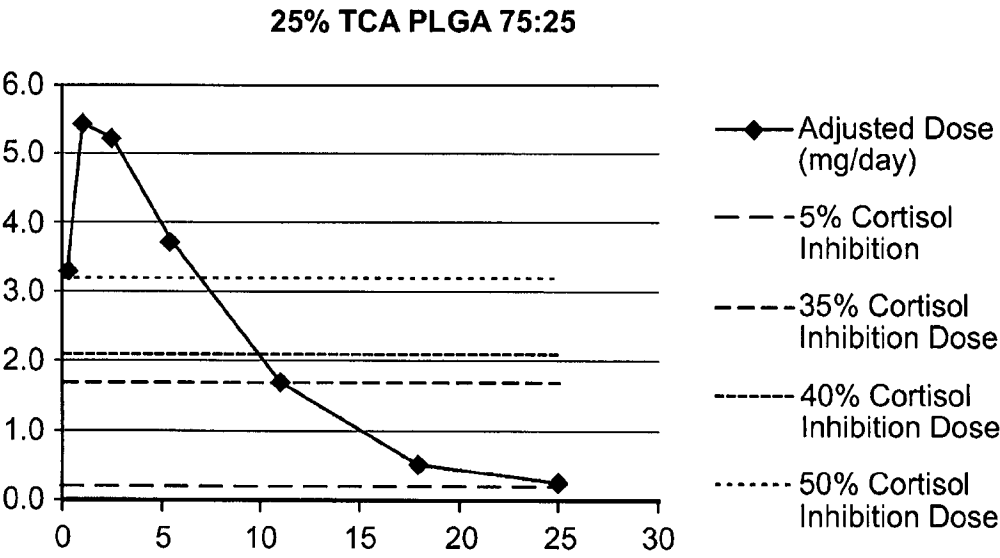


FIG. 6



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FIG. 7

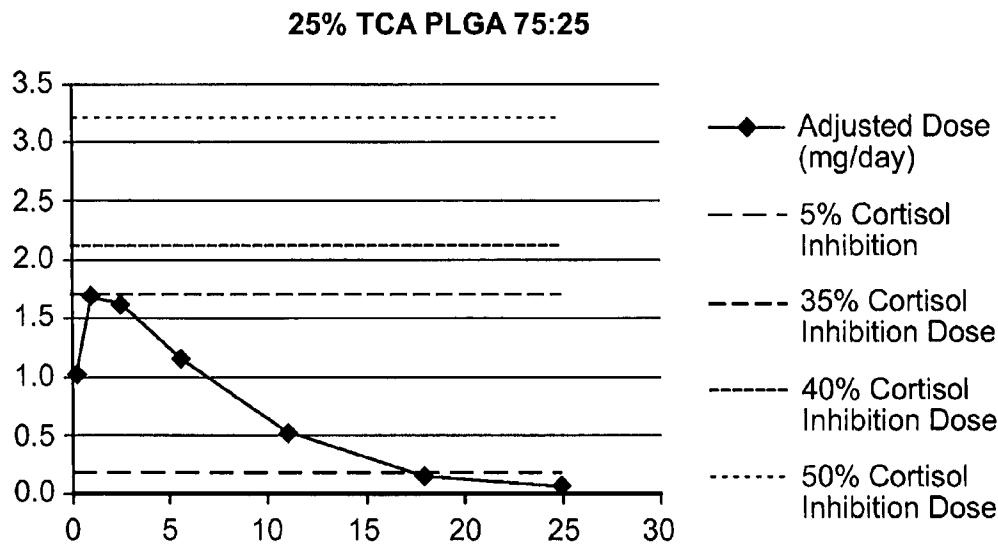
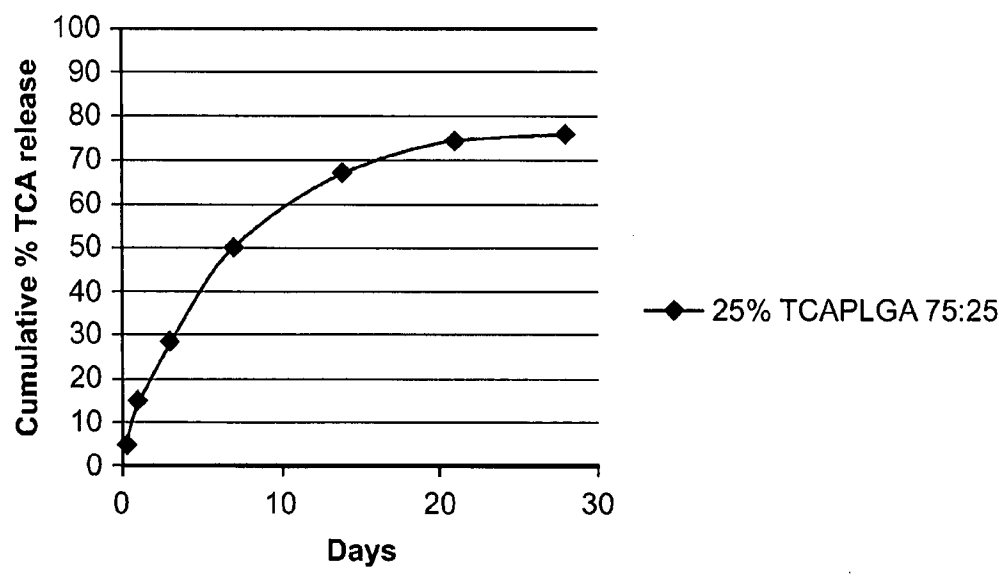


FIG. 8



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FIG. 9

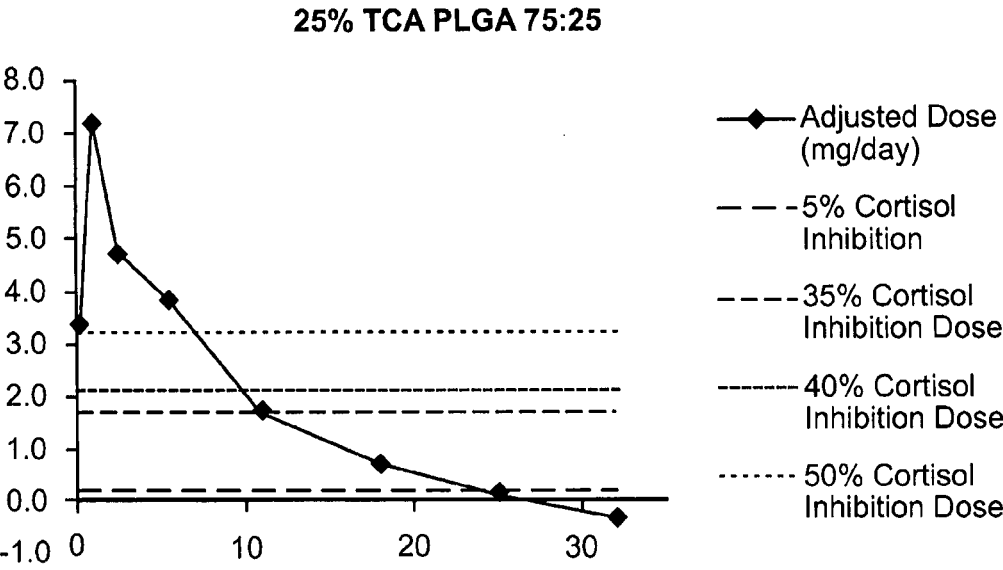
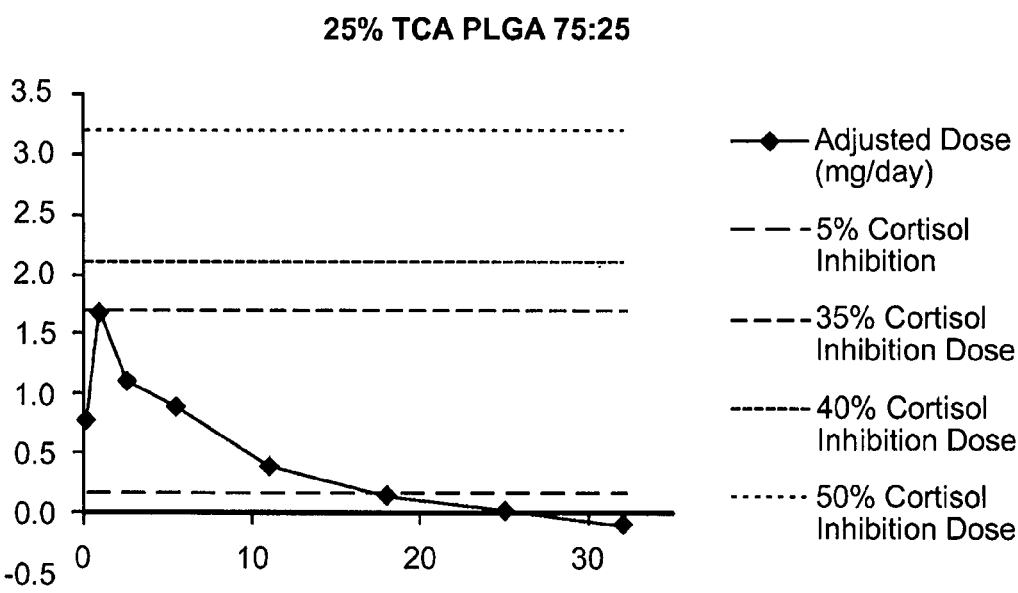


FIG. 10



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FIG. 11

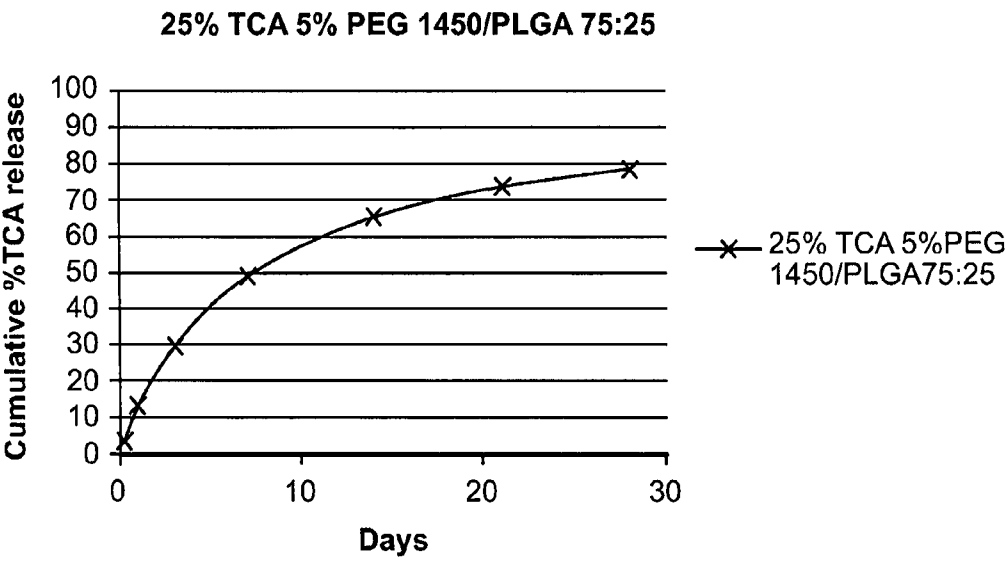
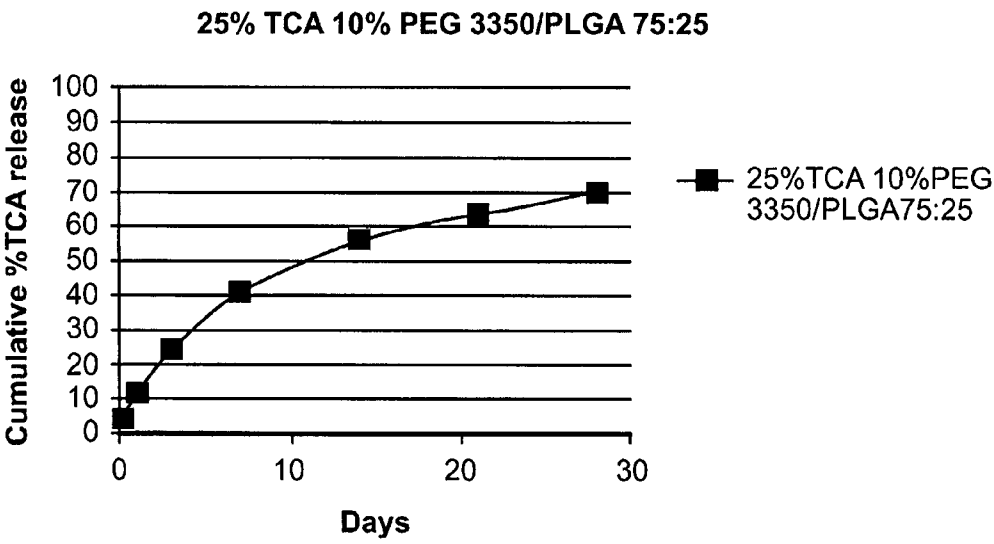


FIG. 12



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FIG. 13

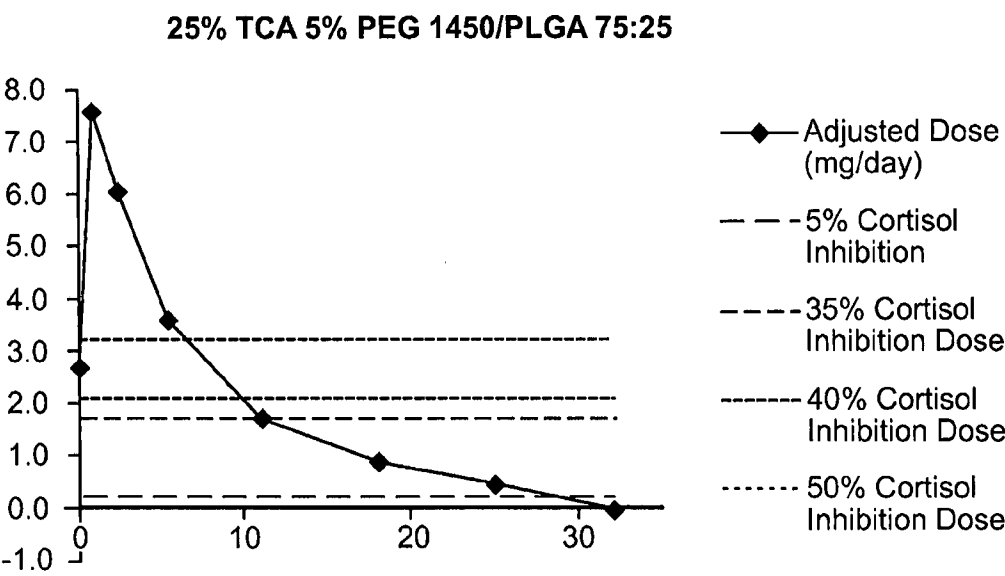
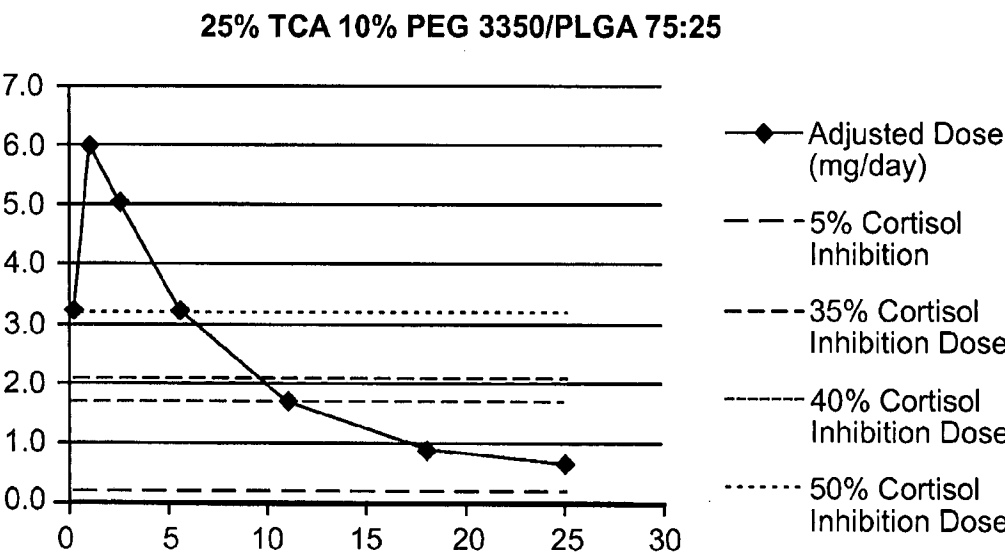


FIG. 14



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FIG. 15

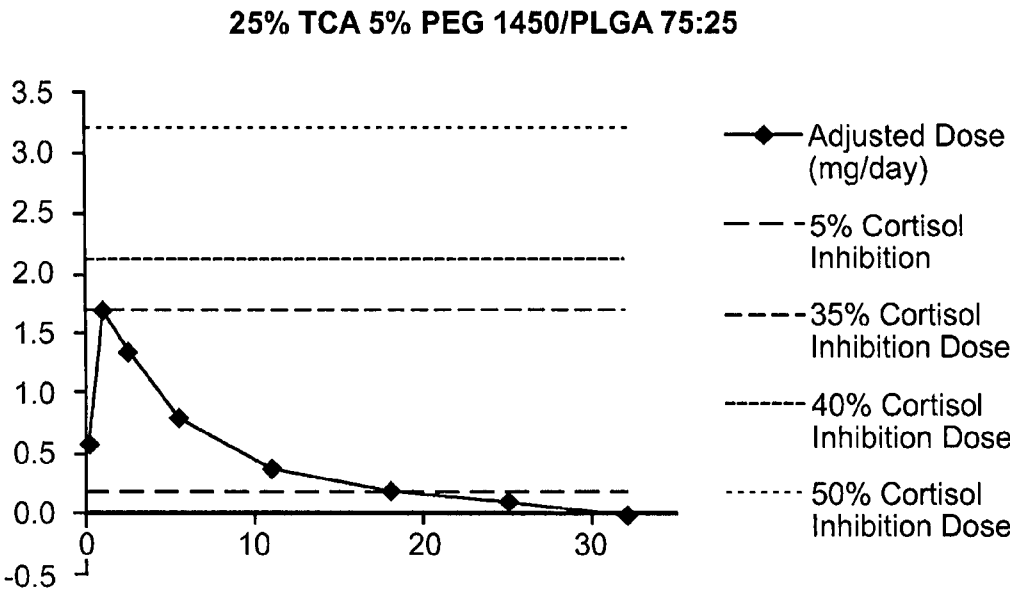


FIG. 16

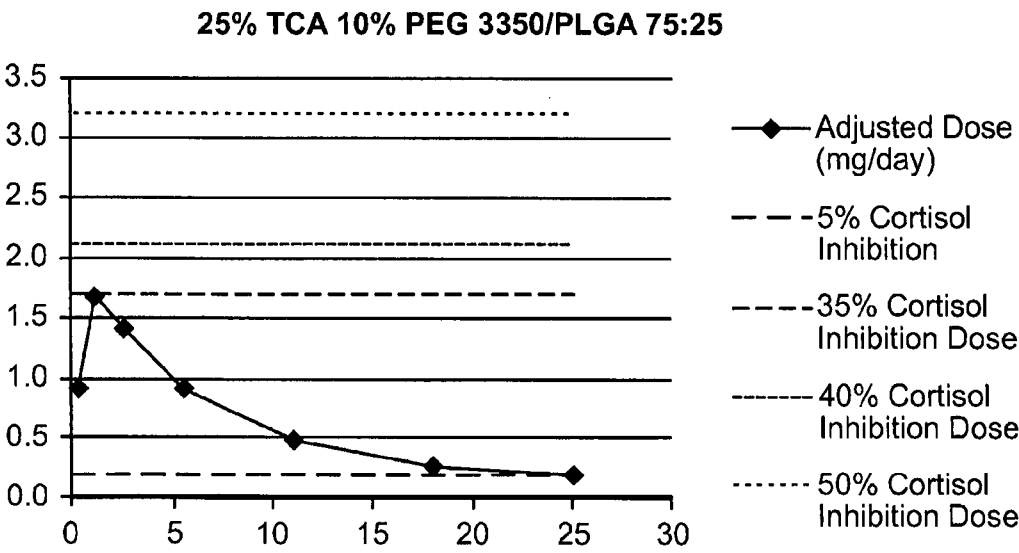


FIG. 17

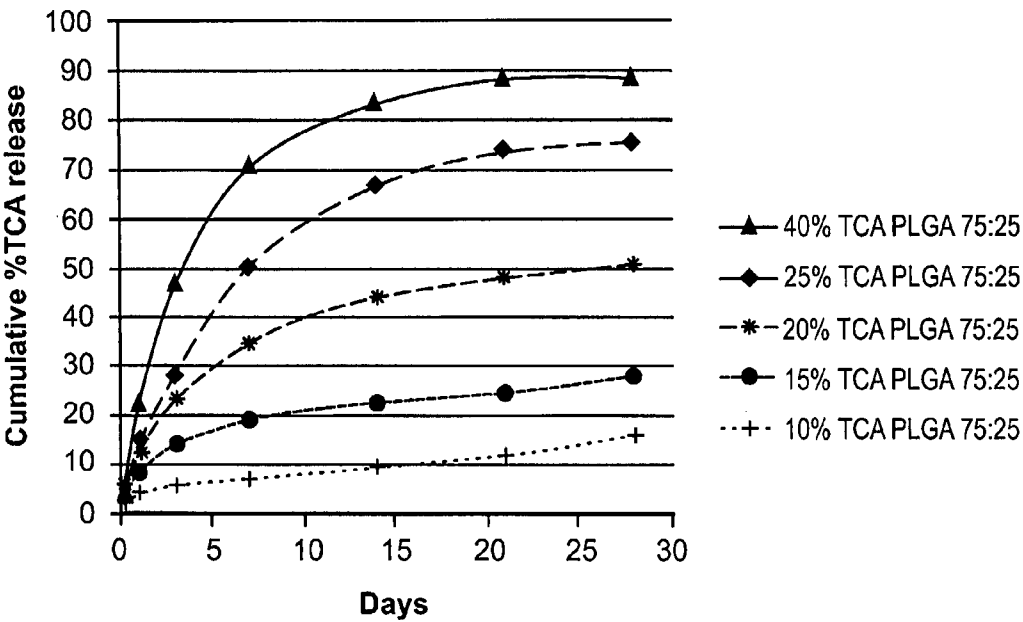


FIG. 18

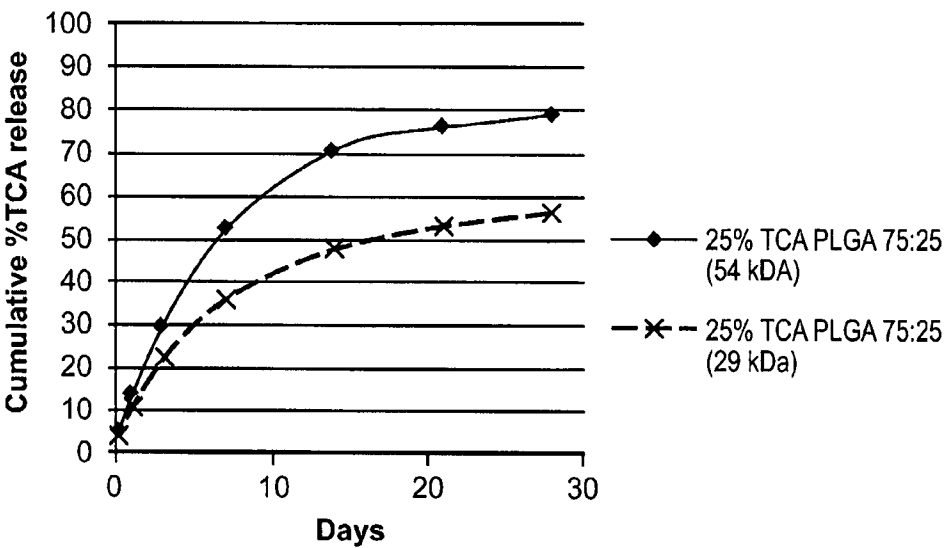


FIG. 19

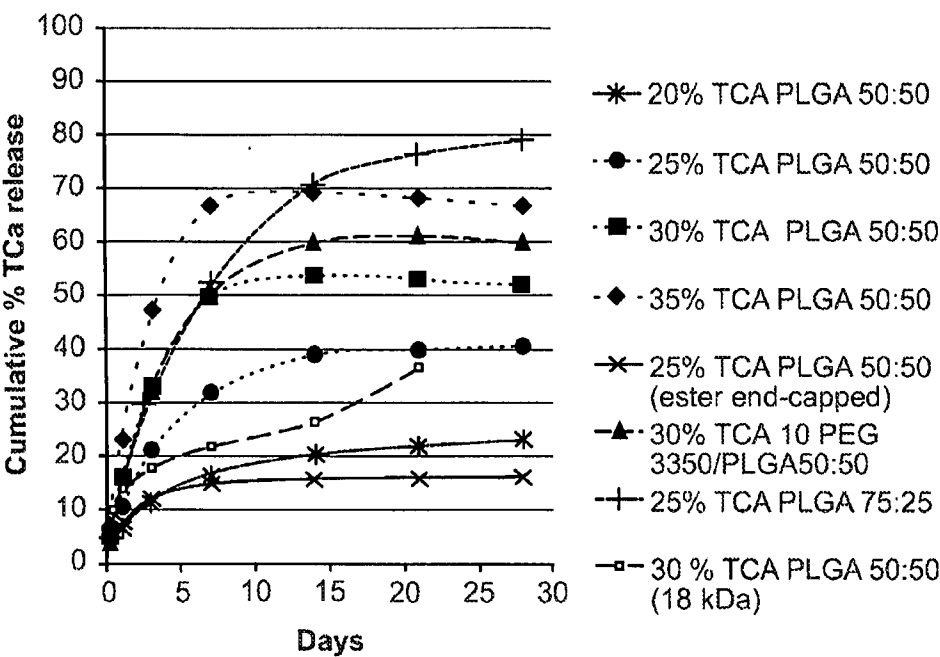
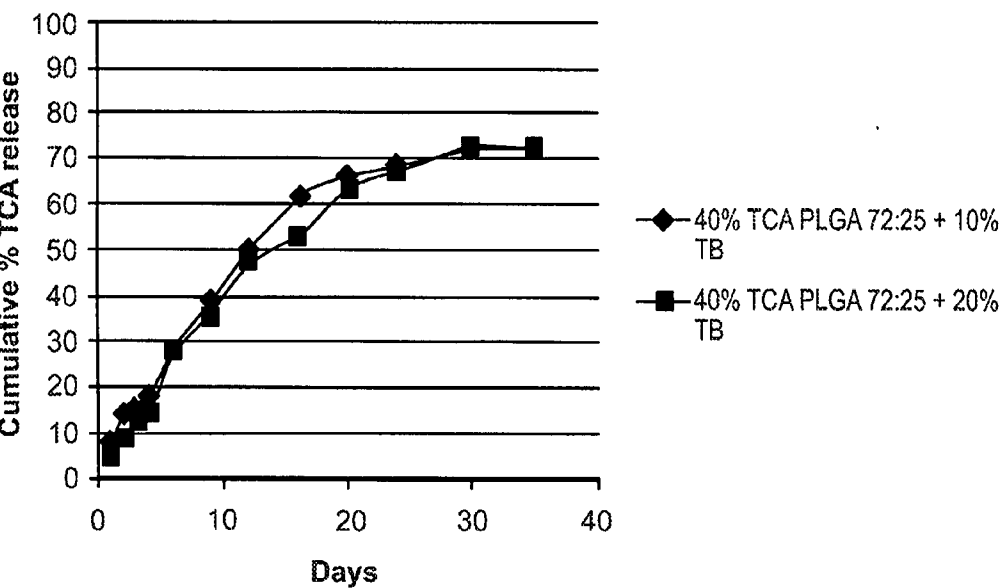


FIG. 20

40% TCA PLGA 75:25 plus Triblock



45
47

FIG. 21

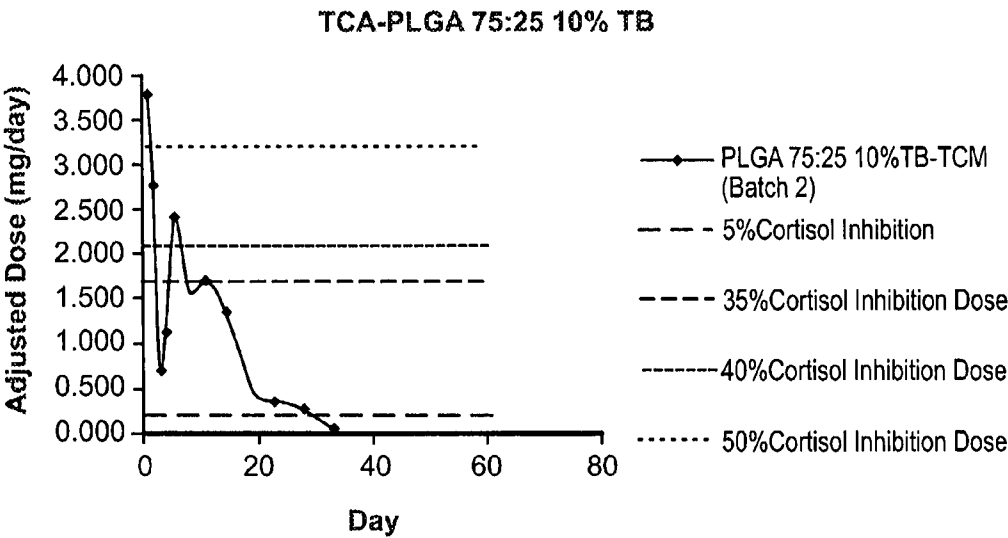


FIG. 22

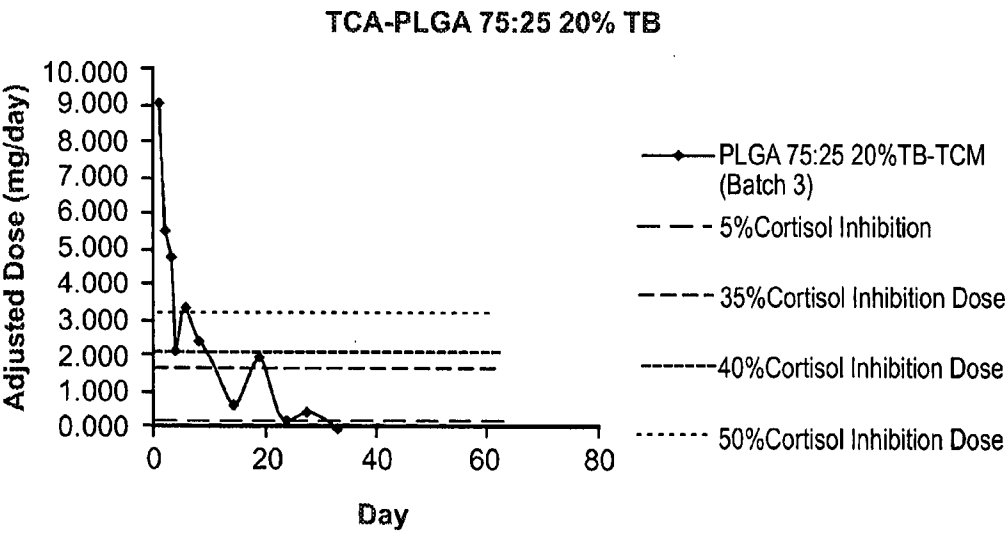


FIG. 23

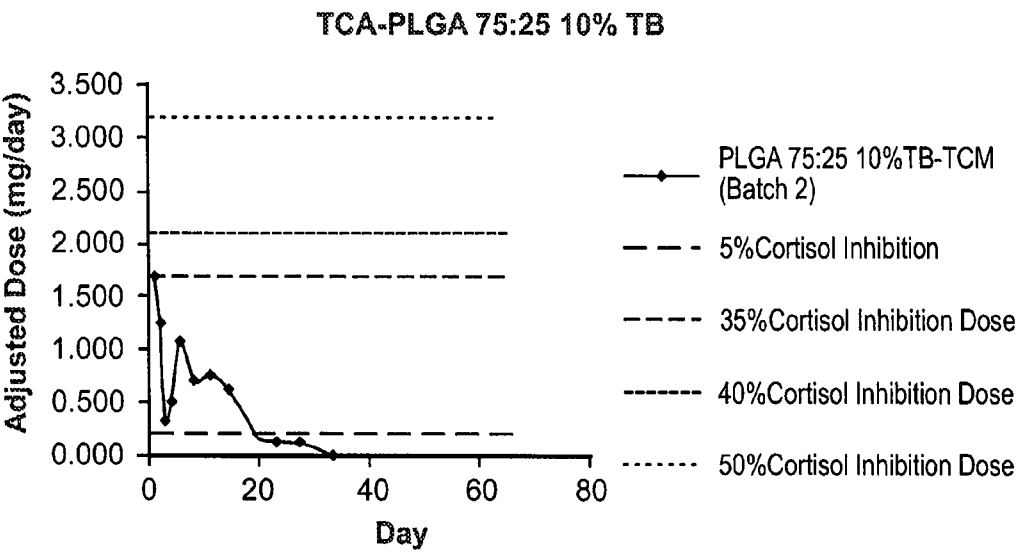
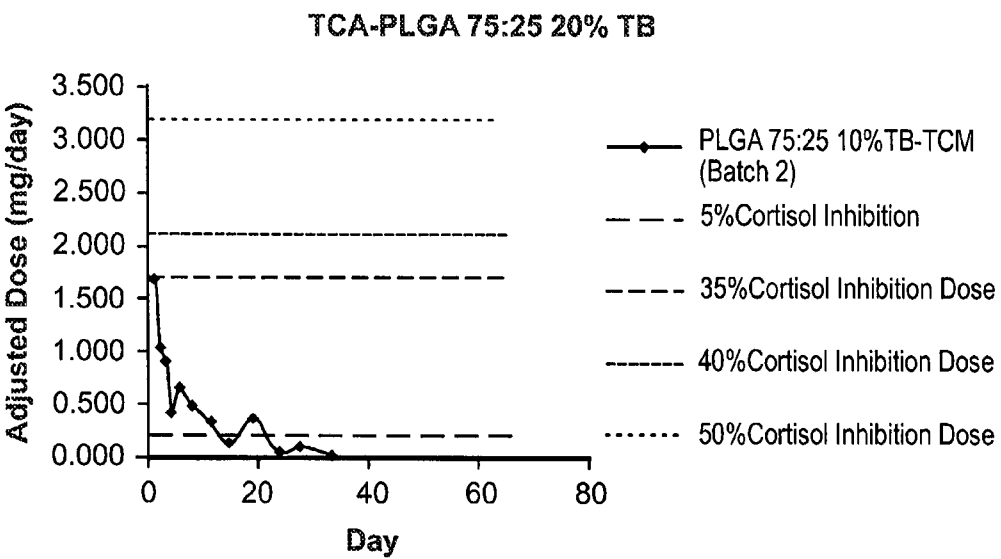


FIG. 24



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FIG. 25

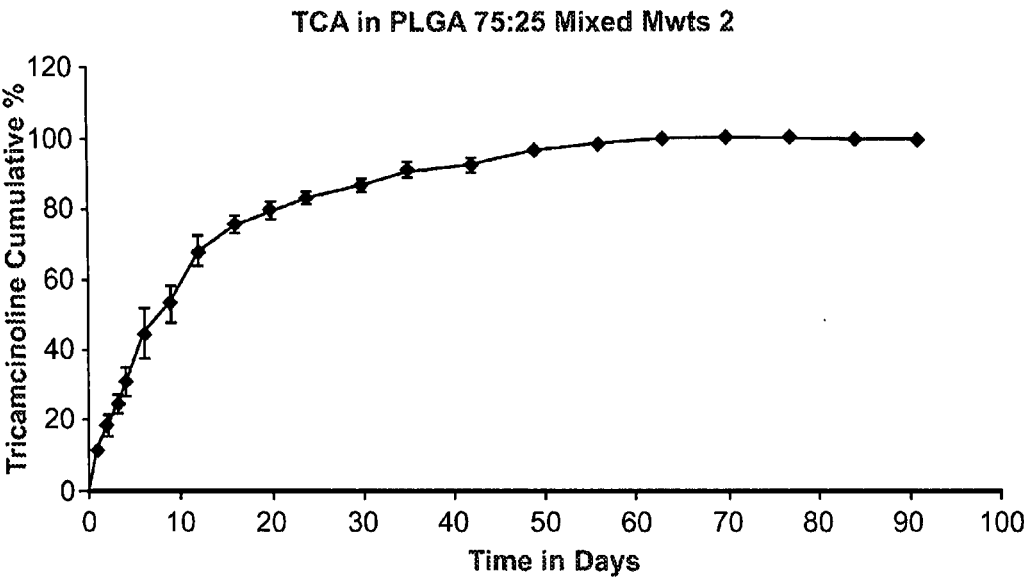


FIG. 26

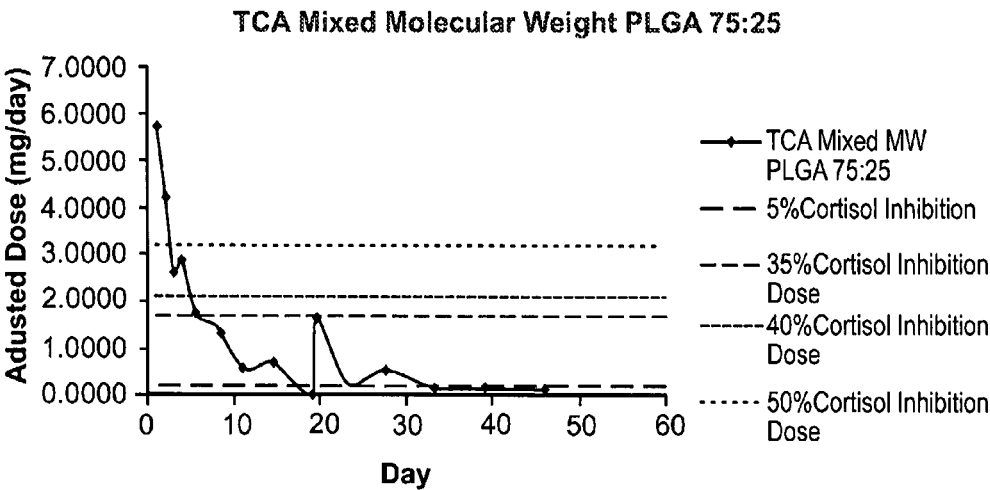


FIG. 27

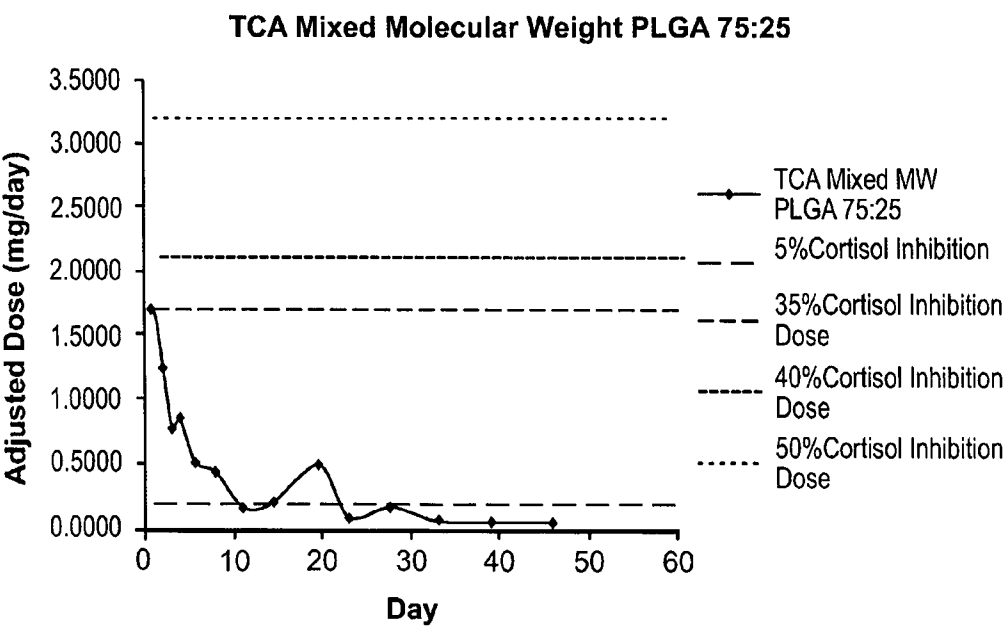
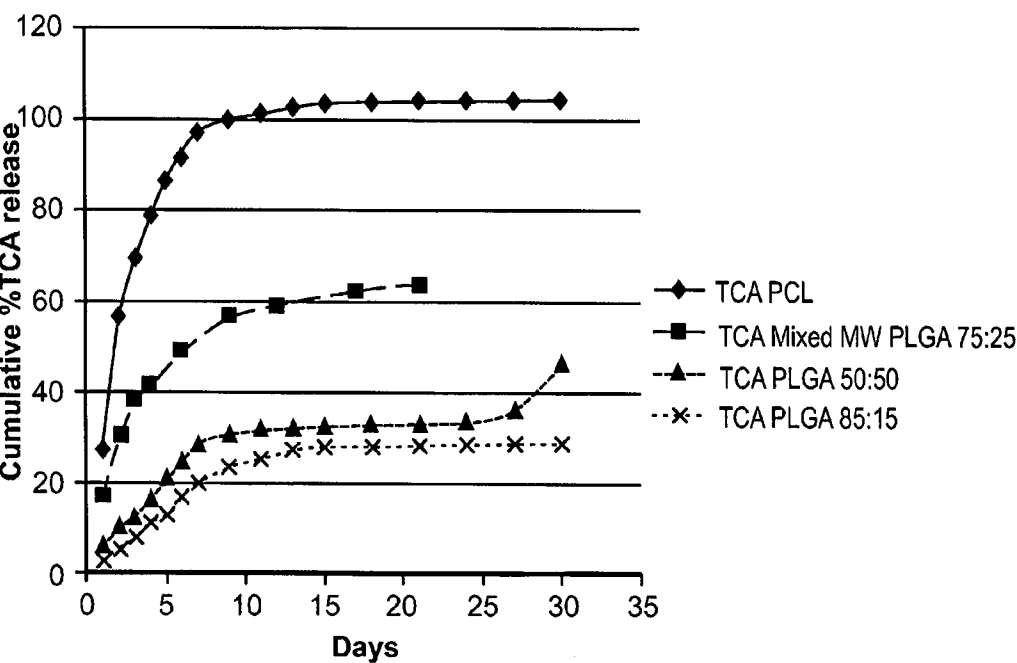


FIG. 28



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FIG. 29

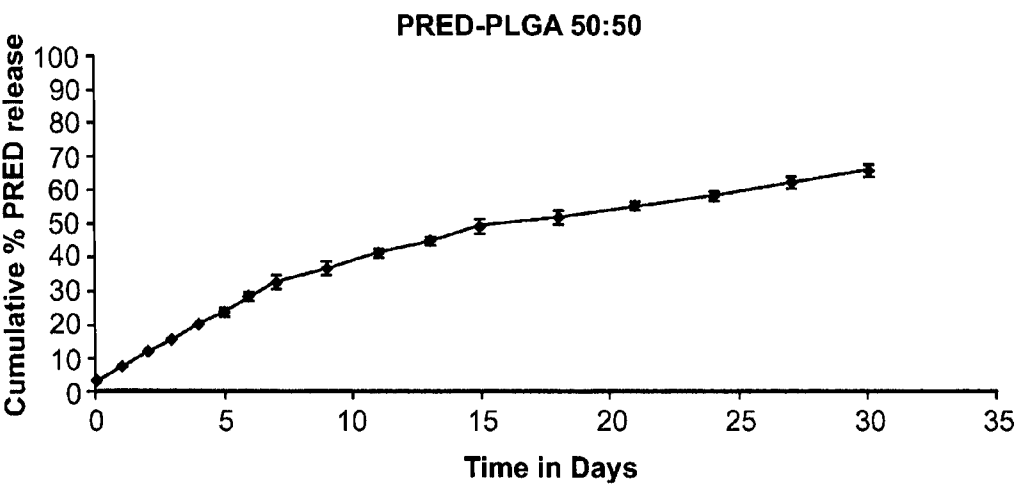
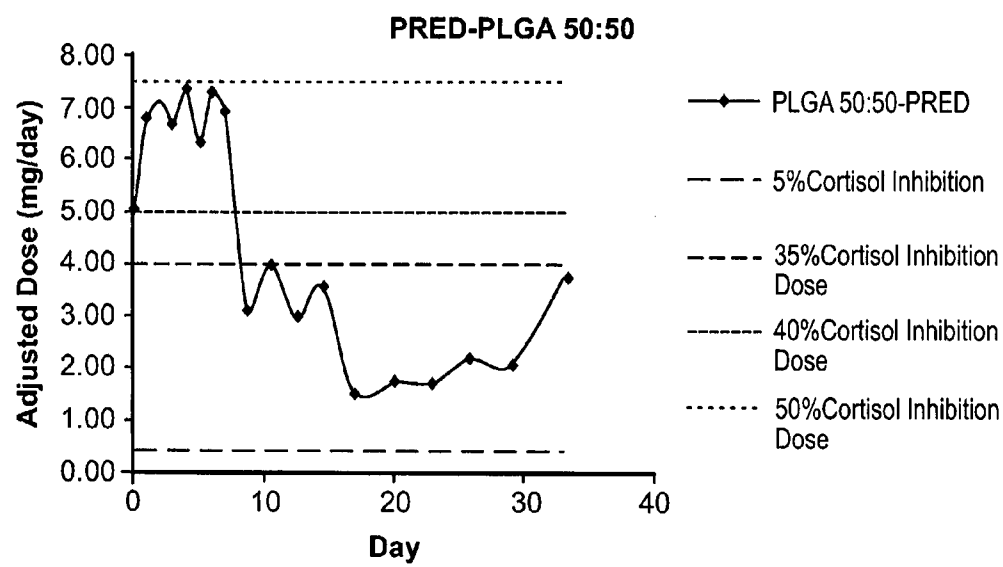


FIG. 30



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FIG. 31

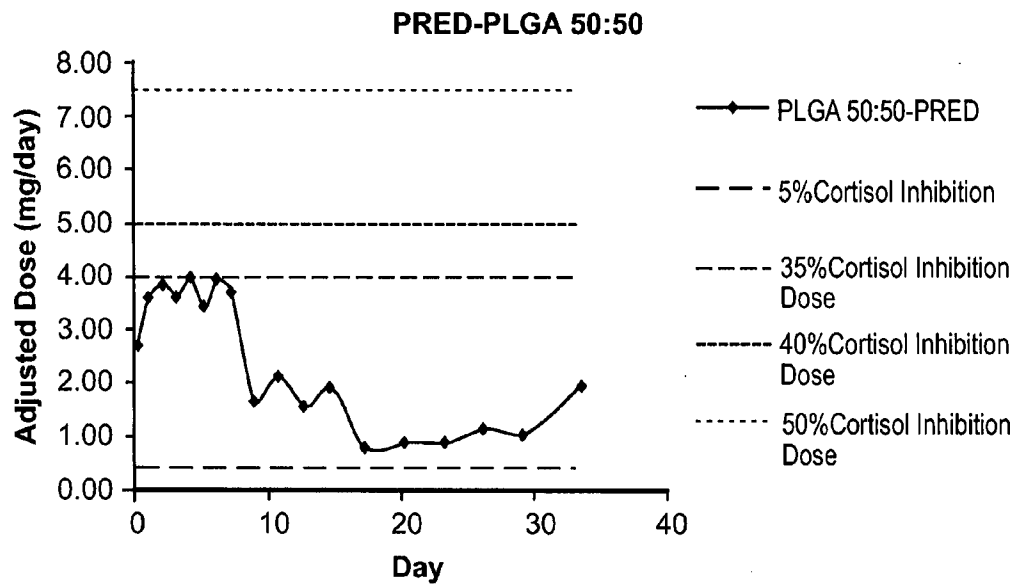
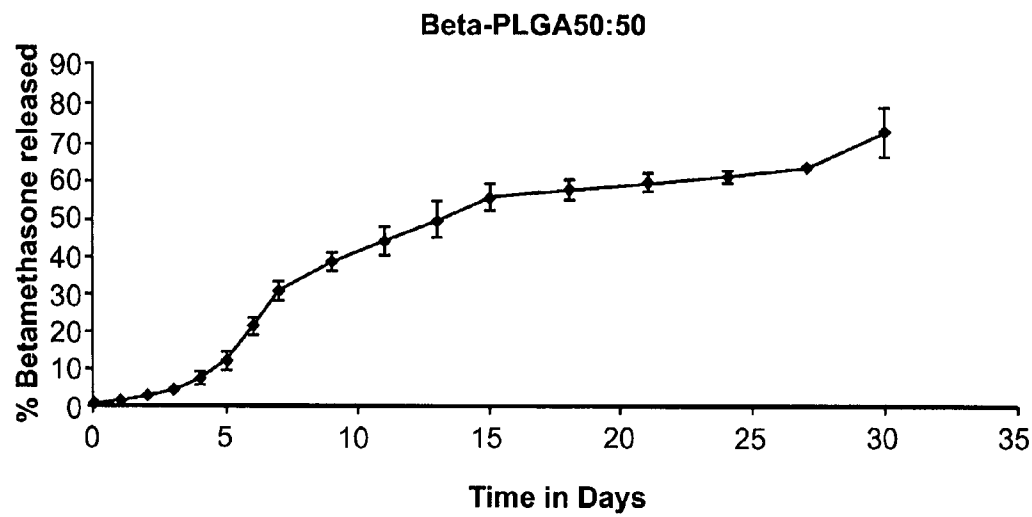


FIG. 32



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FIG. 33

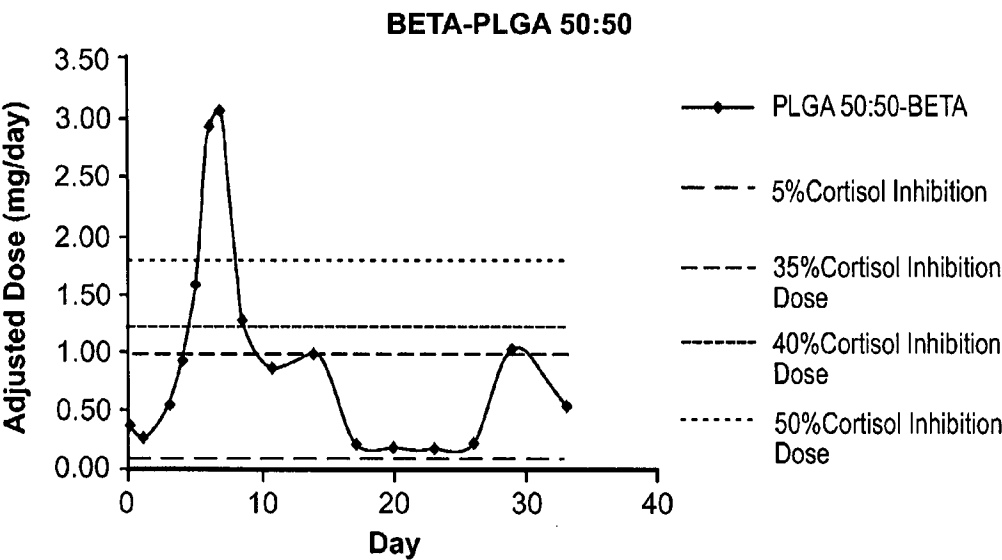
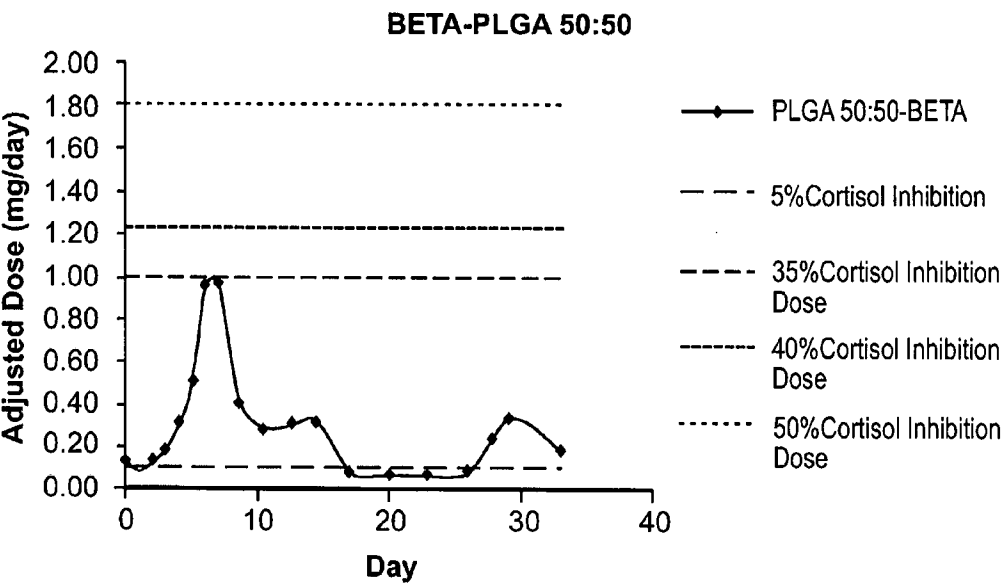


FIG. 34



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FIG. 35

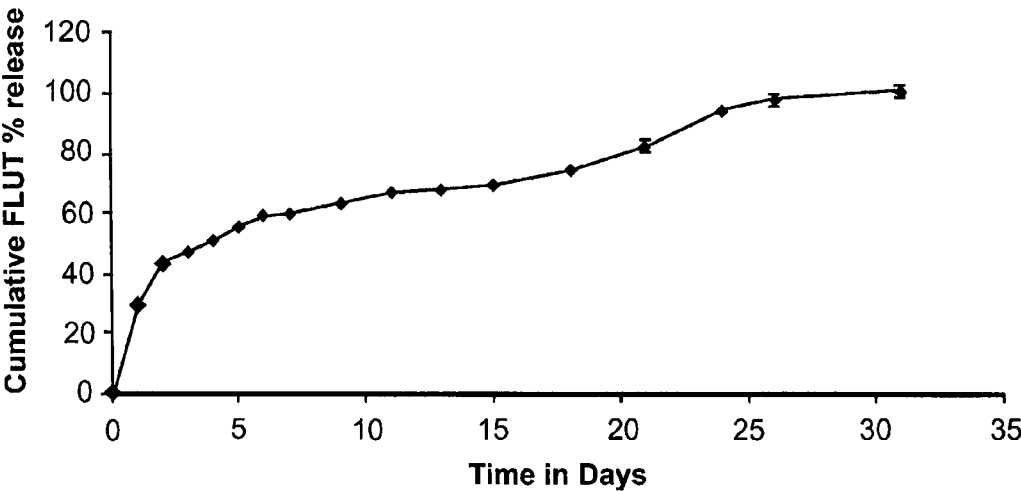


FIG. 36

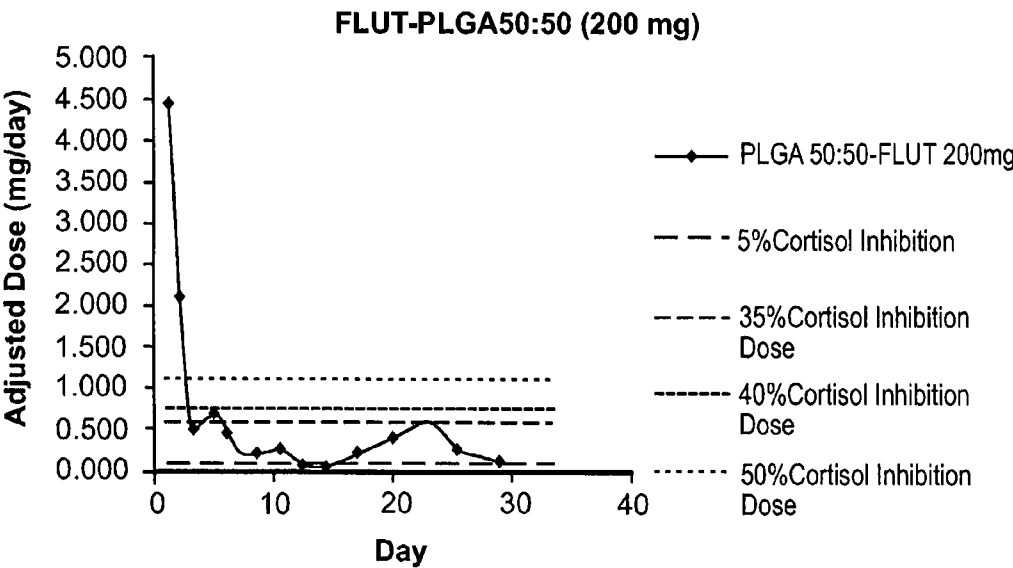


FIG. 37

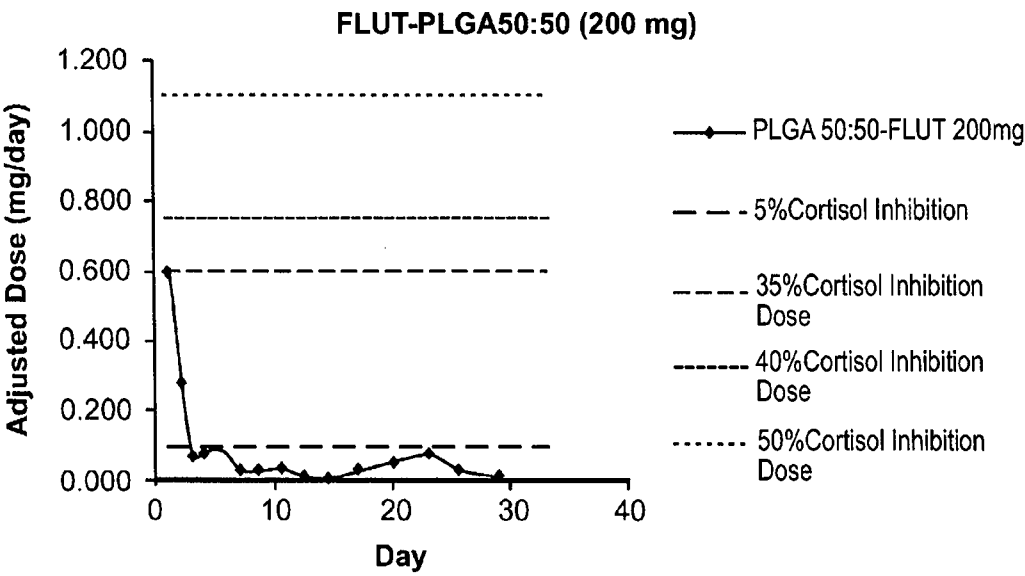
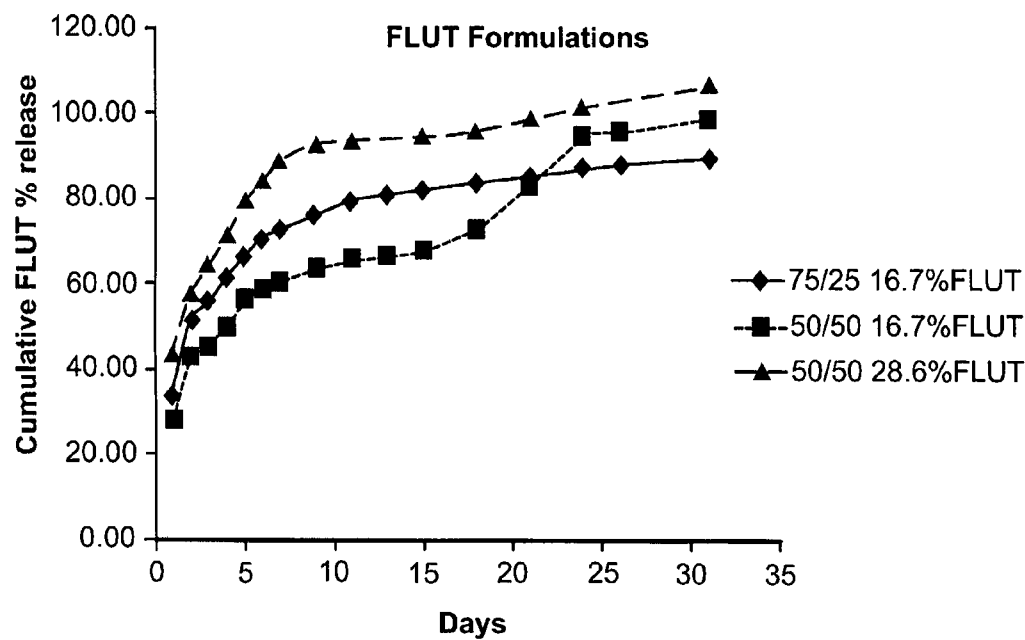


FIG. 38



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FIG. 39

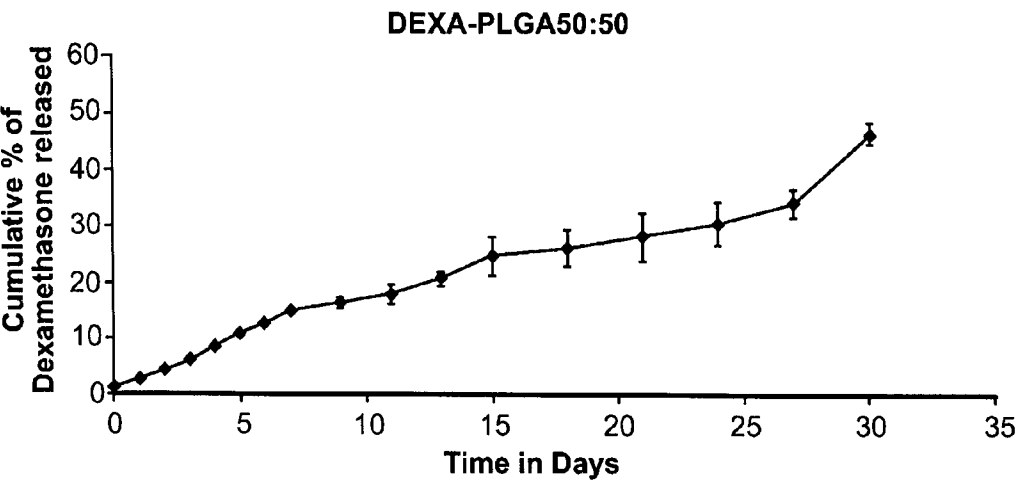


FIG. 40

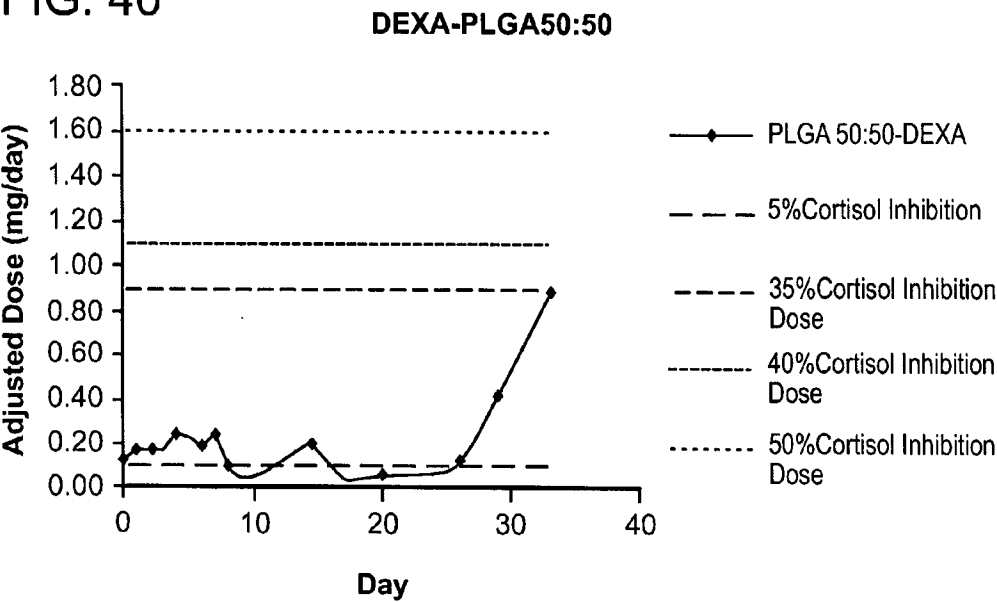


FIG. 41A

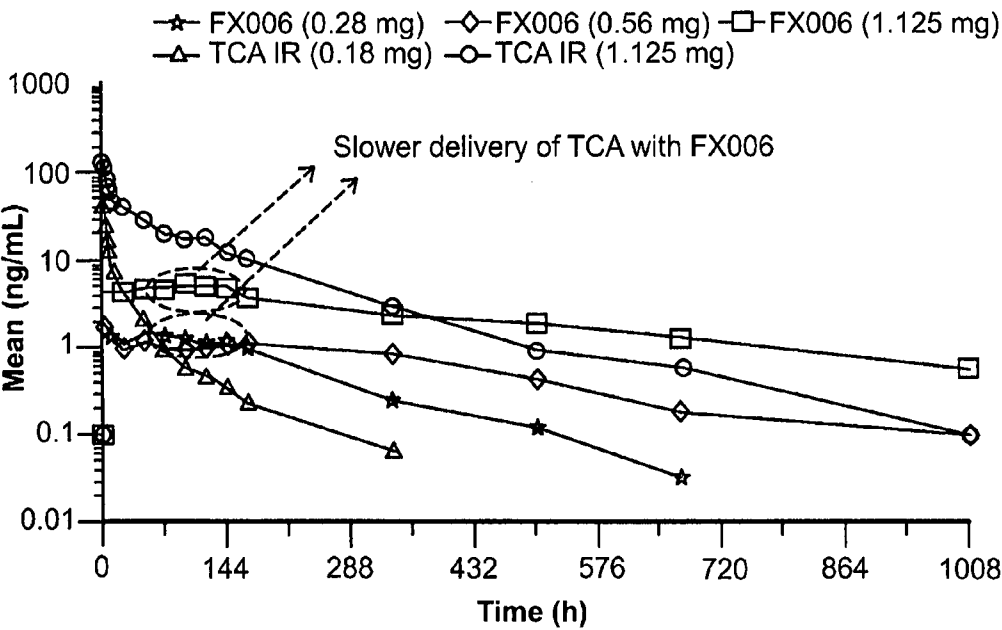
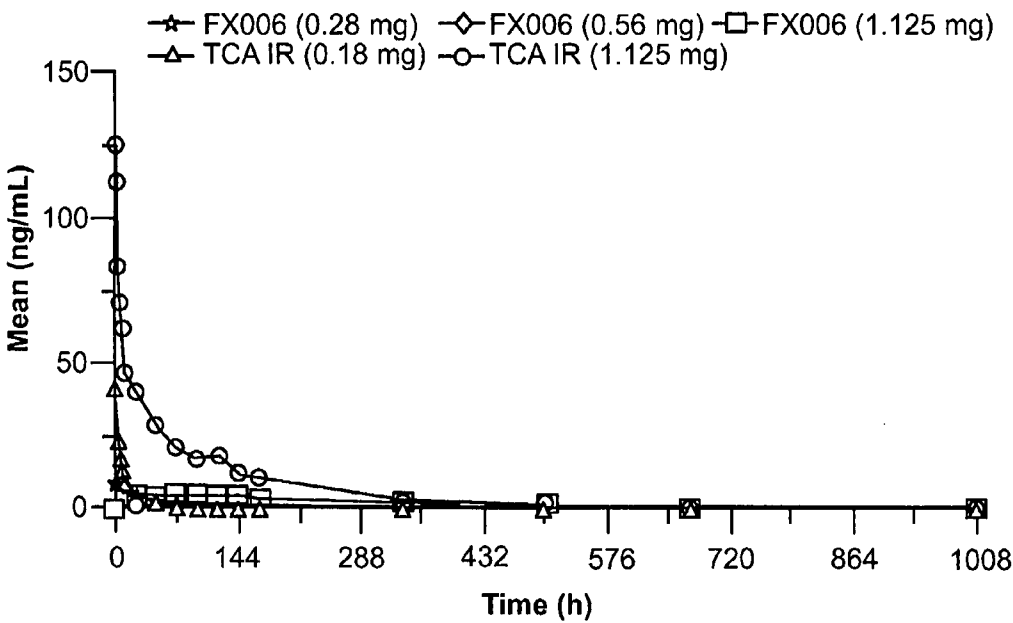


FIG. 41B



86
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FIG. 41C

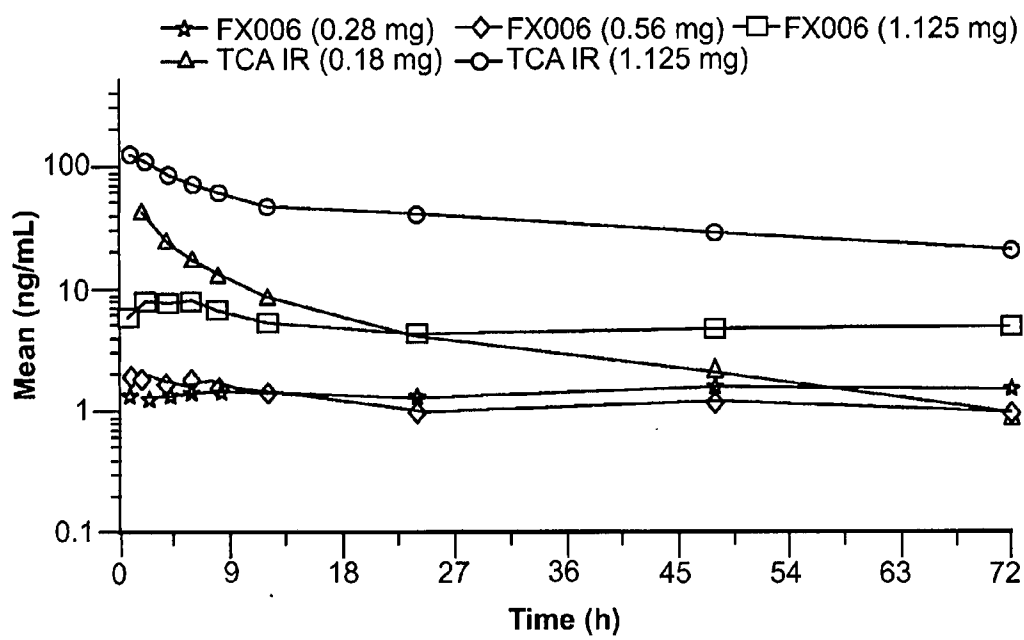


FIG. 41D

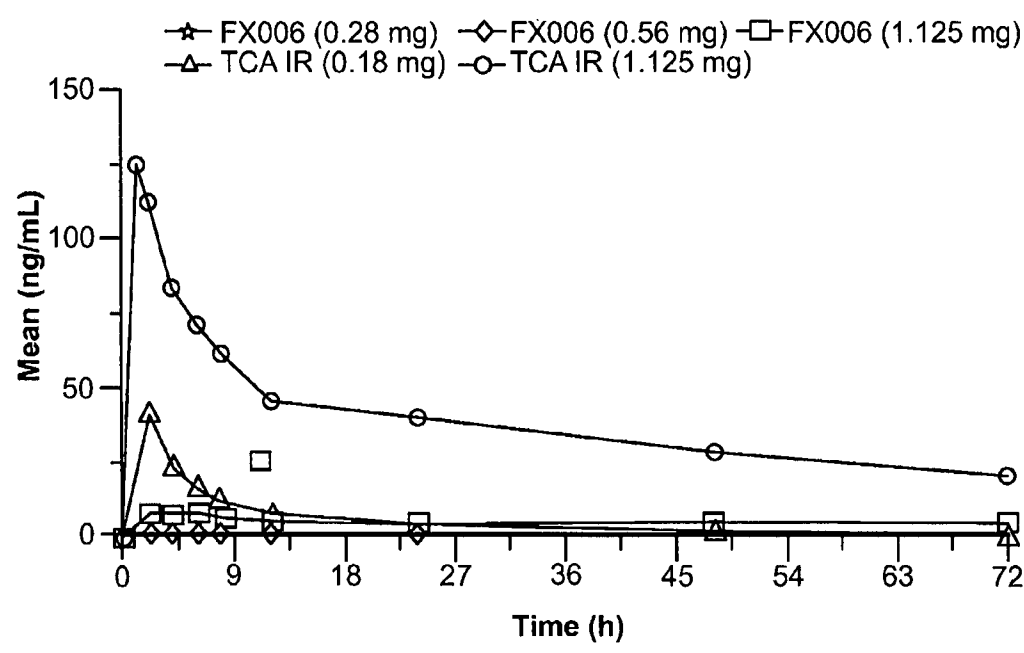


FIG. 42

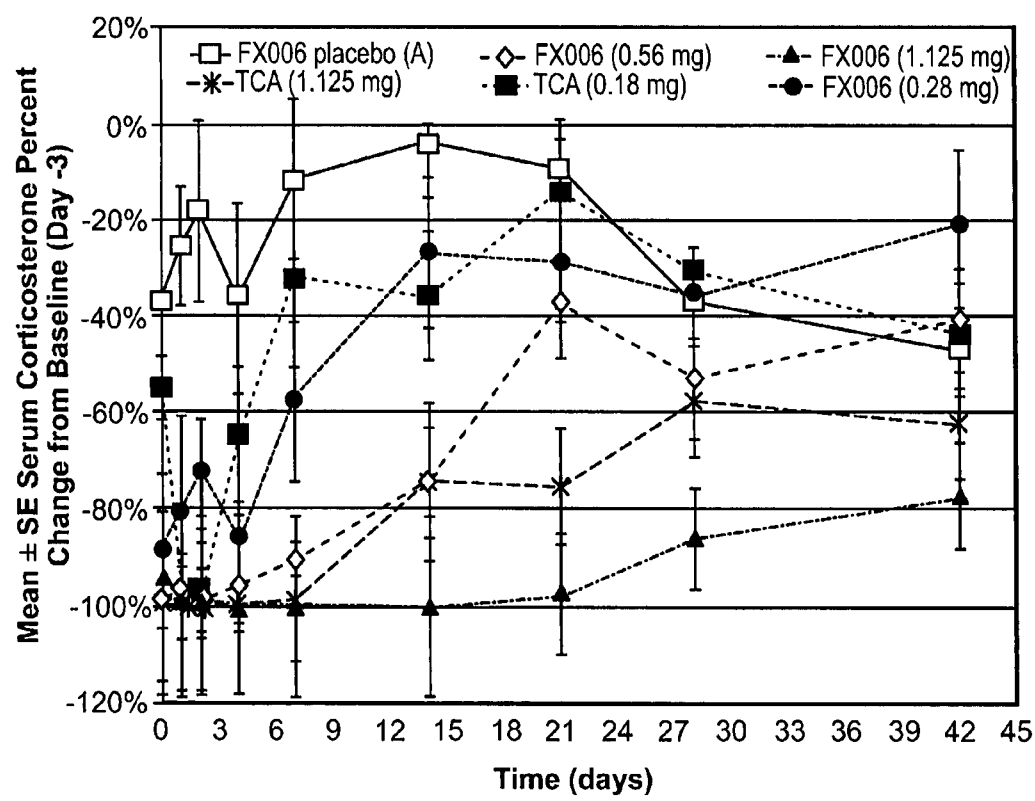


FIG. 43

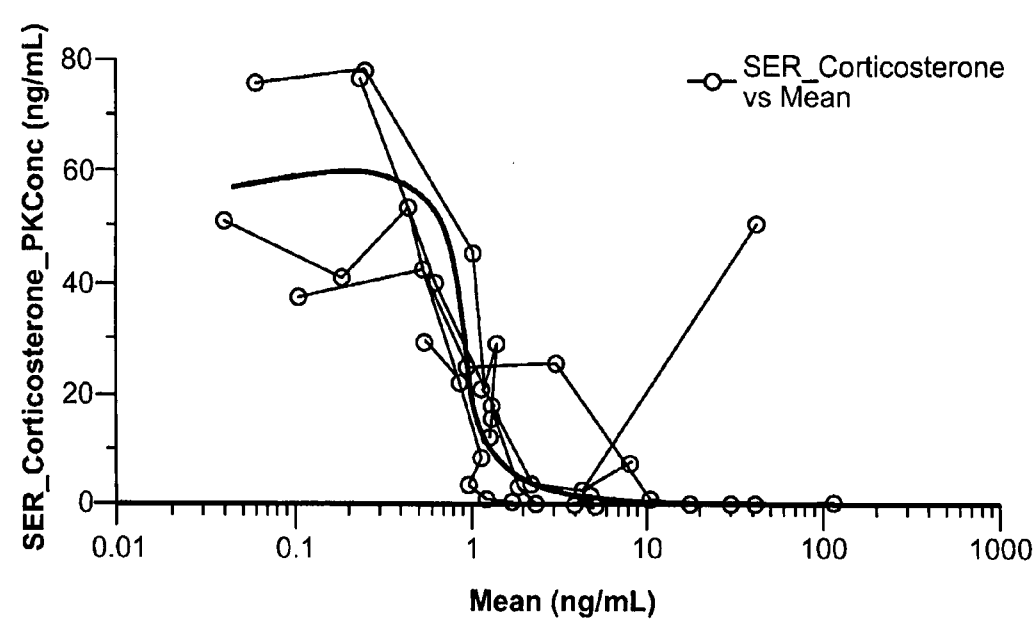


FIG. 44A

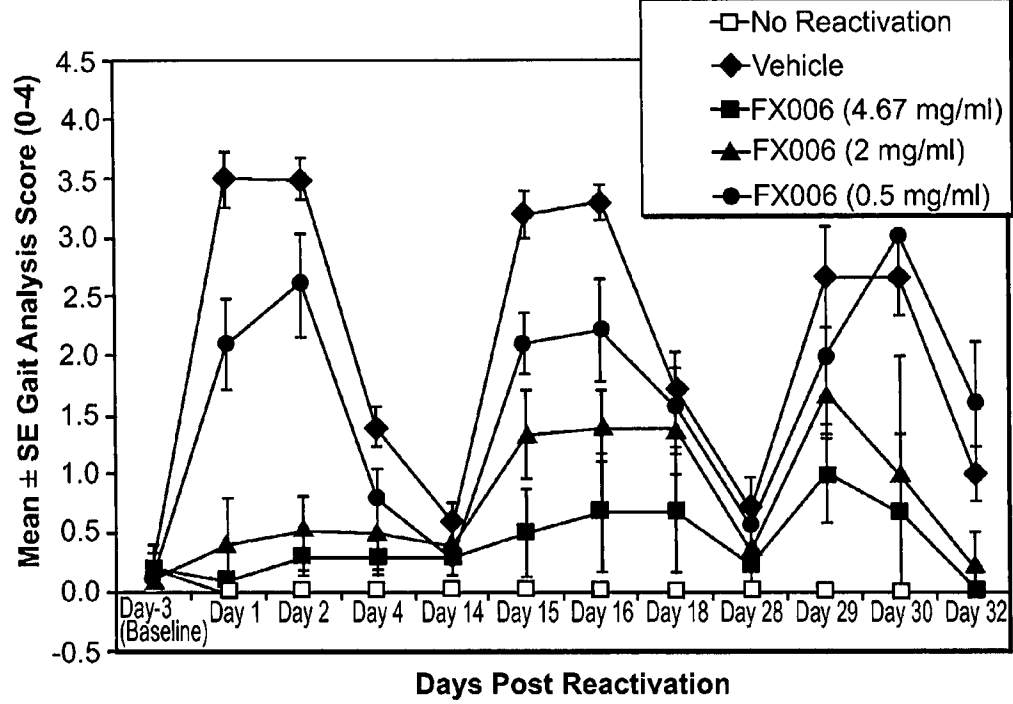
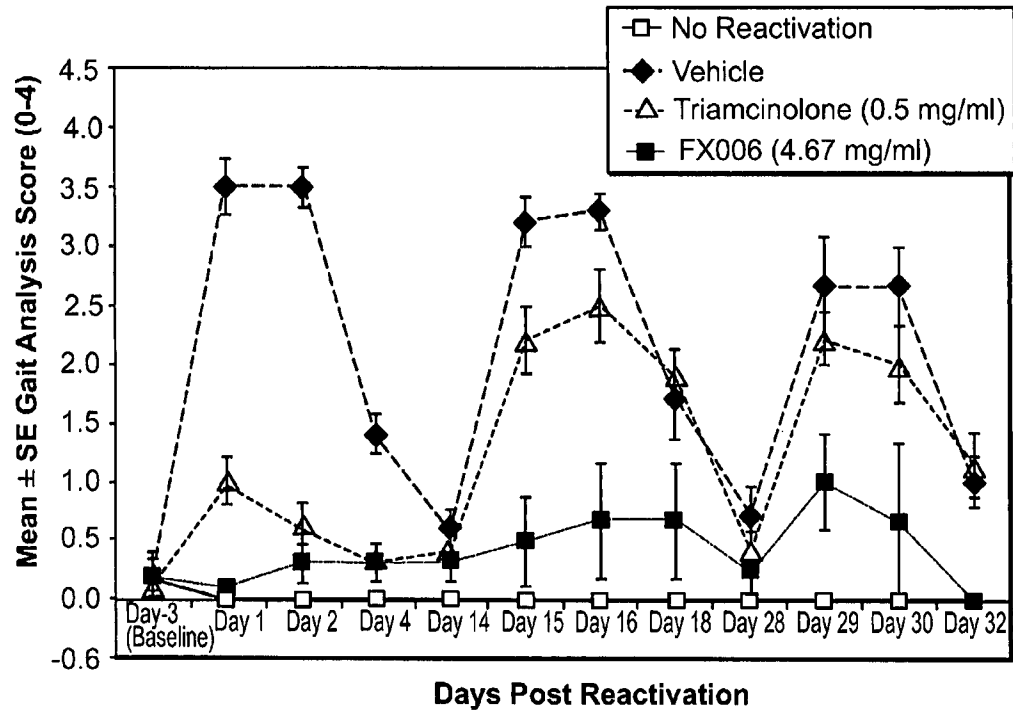


FIG. 44B



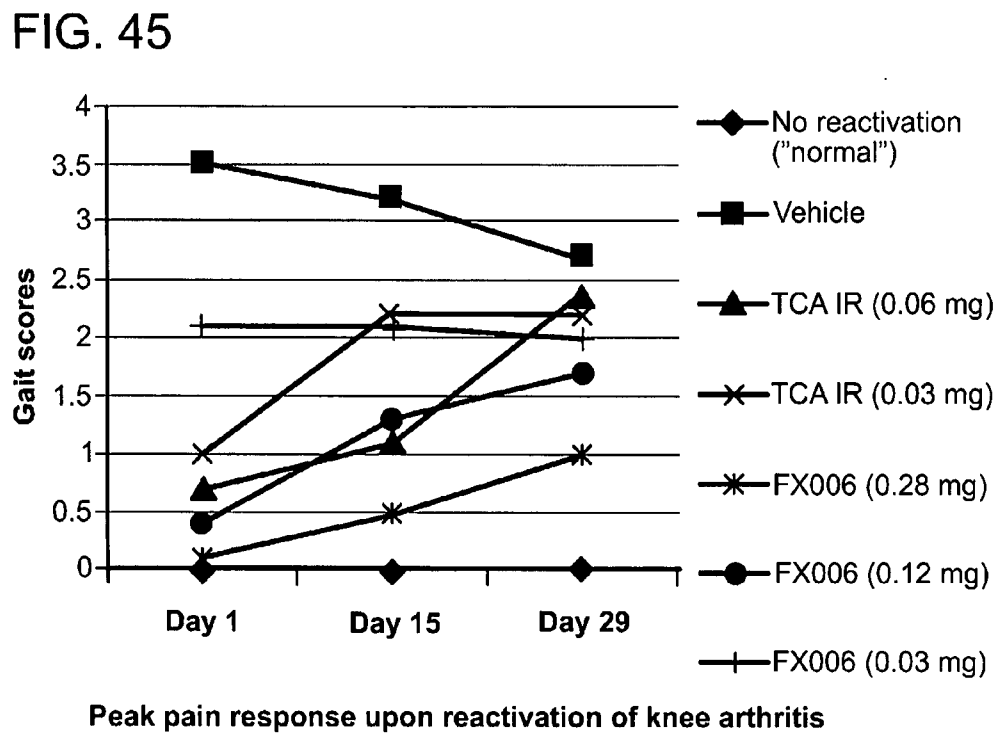
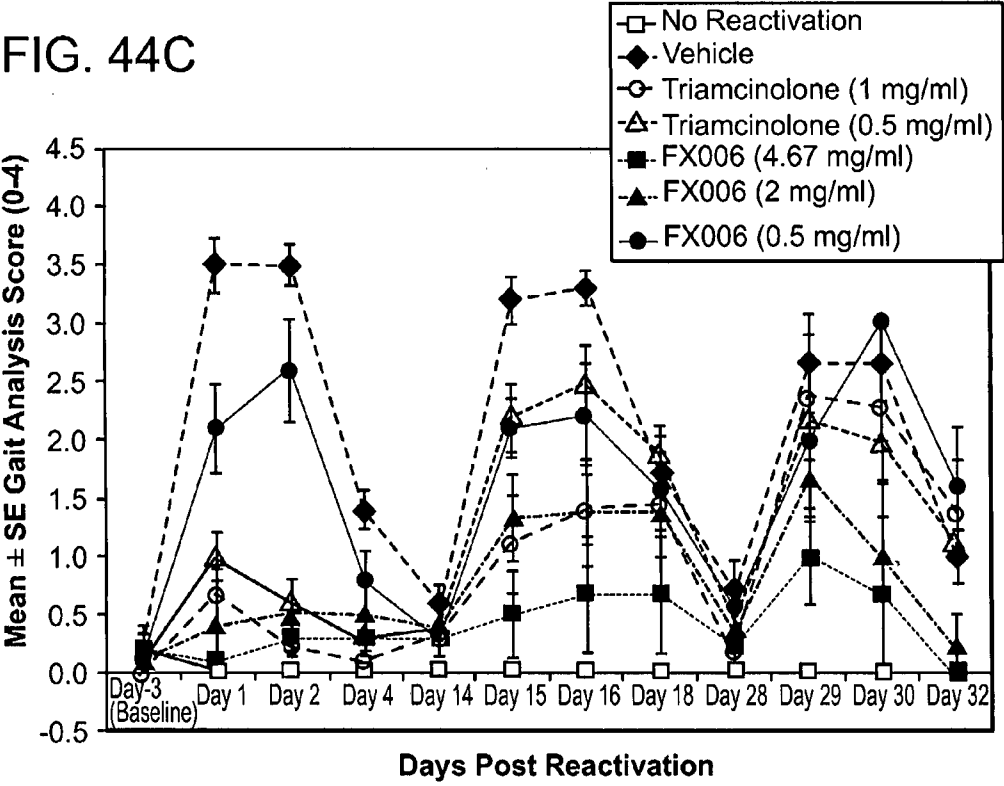


FIG. 46

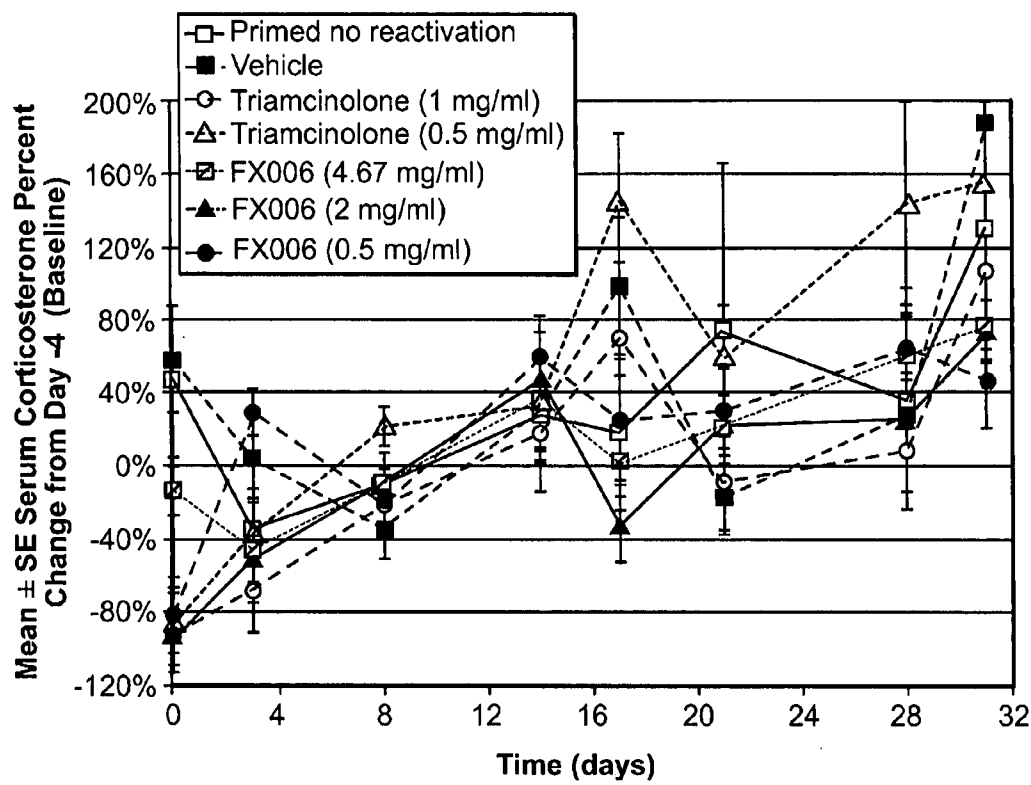


FIG. 47A

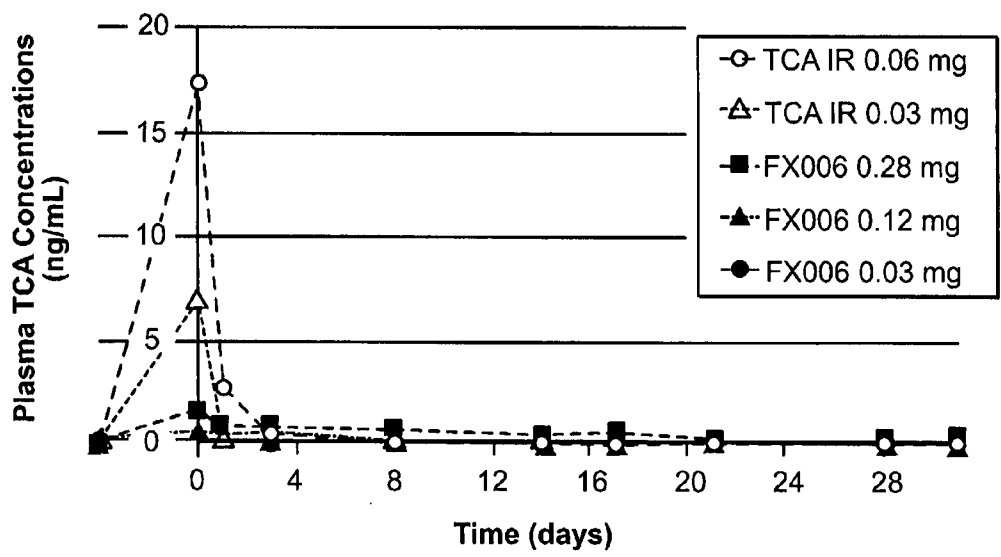


FIG. 47B

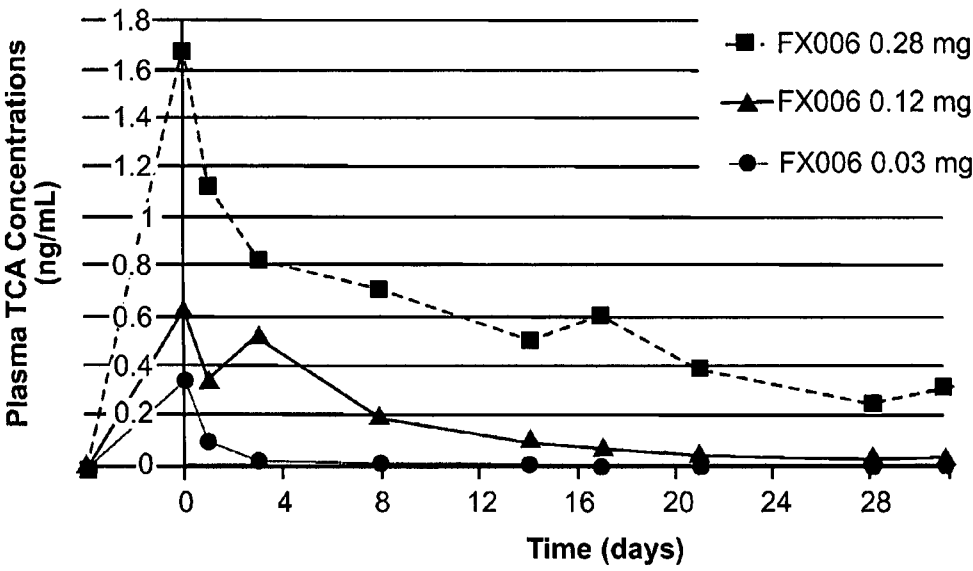
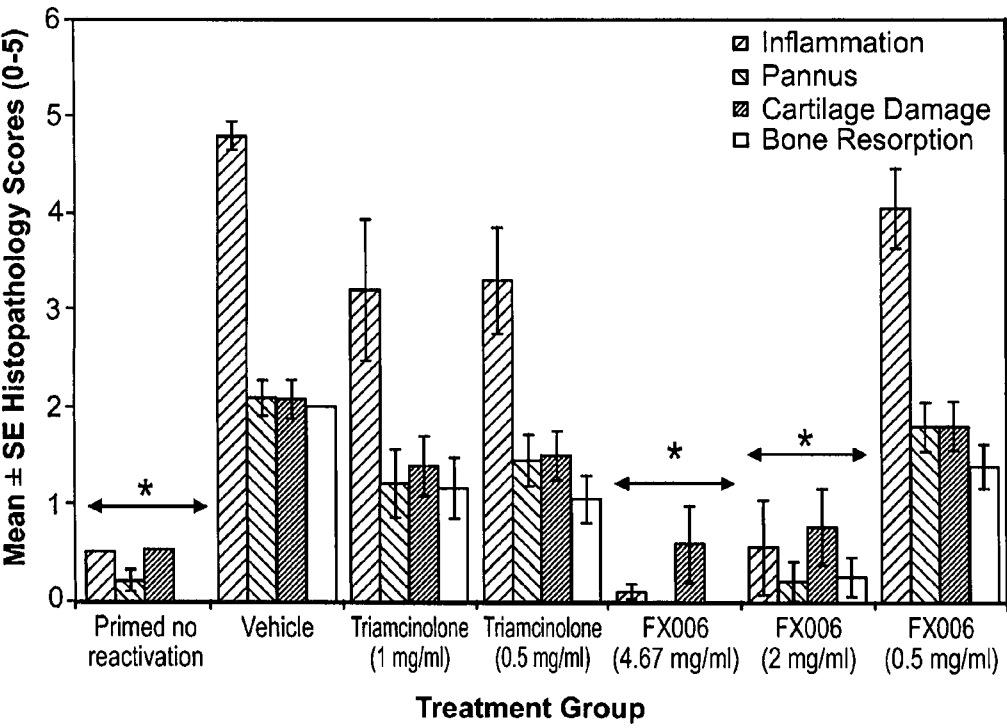


FIG. 48



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CORTICOSTEROIDS FOR THE TREATMENT
OF JOINT PAIN

RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 13/198,168, filed Aug. 4, 2011 claims the benefit of U.S. Provisional Application No. 61/370,666, filed Aug. 4, 2010. The contents of this application are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

This invention relates to the use of corticosteroids to treat pain, including pain caused by inflammatory diseases such as osteoarthritis or rheumatoid arthritis, and to slow, arrest or reverse structural damage to tissues caused by an inflammatory disease, for example damage to articular and/or peri-articular tissues caused by osteoarthritis or rheumatoid arthritis. More specifically, a corticosteroid is administered locally as a sustained release dosage form (with or without an immediate release component) that results in efficacy accompanied by clinically insignificant or no measurable effect on endogenous cortisol production.

BACKGROUND OF THE INVENTION

Corticosteroids influence all tissues of the body and produce various cellular effects. These steroids regulate carbohydrate, lipid, protein biosynthesis and metabolism, and water and electrolyte balance. Corticosteroids influencing cellular biosynthesis or metabolism are referred to as glucocorticoids while those affecting water and electrolyte balance are mineralocorticoids. Both glucocorticoids and mineralocorticoids are released from the cortex of the adrenal gland.

The administration of corticosteroids, particularly for extended periods of time, can have a number of unwanted side effects. The interdependent feedback mechanism between the hypothalamus, which is responsible for secretion of corticotrophin-releasing factor, the pituitary gland, which is responsible for secretion of adrenocorticotropic hormone, and the adrenal cortex, which secretes cortisol, is termed the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis may be suppressed by the administration of corticosteroids, leading to a variety of unwanted side effects.

Accordingly, there is a medical need to extend the local duration of action of corticosteroids, while reducing the systemic side effects associated with that administration. Thus, there is a need in the art for methods and compositions for the sustained local treatment of pain and inflammation, such as joint pain, with corticosteroids that results in clinically insignificant or no measurable HPA axis suppression. In addition, there is a medical need to slow, arrest, reverse or otherwise inhibit structural damage to tissues caused by inflammatory diseases such as damage to articular tissues resulting from osteoarthritis or rheumatoid arthritis.

SUMMARY OF THE INVENTION

Described herein are compositions and methods for the treatment of pain and inflammation using corticosteroids. The compositions and methods provided herein use one or more corticosteroids in a microparticle formulation. The corticosteroid microparticle formulations provided herein are effective at treating pain and/or inflammation with minimal long-term side effects of corticosteroid administration, including for example, prolonged suppression of the HPA axis. The

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corticosteroid microparticle formulations are suitable for administration, for example, local administration by injection into a site at or near the site of a patient's pain and/or inflammation. The corticosteroid microparticle formulations provided herein are effective in slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease with minimal long-term side effects of corticosteroid administration, including for example, prolonged suppression of the HPA axis. The corticosteroid microparticle formulations are suitable for administration, for example, local administration by injection into a site at or near the site of structural tissue damage. As used herein, "prolonged" suppression of the HPA axis refers to levels of cortisol suppression greater than 35% by day 14 post-administration, for example post-injection. The corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-injection. In some embodiments, the corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration, for example post-injection. In some embodiments, the corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are negligible at any time post-injection. Thus, the corticosteroid microparticle formulations in these embodiments are effective in the absence of any significant HPA axis suppression. Administration of the corticosteroid microparticle formulations provided herein can result in an initial "burst" of HPA axis suppression, for example, within the first few days, within the first two days and/or within the first 24 hours post-injection, but by day 14 post-injection, suppression of the HPA axis is less than 35%.

In certain embodiments, a sustained release form of corticosteroids is administered locally to treat pain and inflammation. Local administration of a corticosteroid microparticle formulation can occur, for example, by injection into the intra-articular space, peri-articular space, soft tissues, lesions, epidural space, perineural space, or the foramenal space at or near the site of a patient's pain. In certain embodiments, the formulation additionally contains an immediate release component. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space for the treatment of pain, for example, due to osteoarthritis, rheumatoid arthritis, gouty arthritis, bursitis, tenosynovitis, epicondylitis, synovitis or other joint disorder. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into soft tissues or lesions for the treatment of inflammatory disorders, for example, the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses such as psoriasis. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an epidural space, a perineural space, a foramenal space or other spinal space for the treatment of corticosteroid-responsive degenerative musculoskeletal disorders such as Neurogenic Claudication. In certain preferred embodiments of the invention, a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space or into soft tissues to slow, arrest, reverse or otherwise

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inhibit structural damage to tissues associated with progressive disease such as, for example, the damage to cartilage associated with progression of osteoarthritis.

In certain embodiments of the invention, a combination of an immediate release form and a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space for the treatment of pain, for example, due to osteoarthritis, rheumatoid arthritis or other joint disorder(s). In certain embodiments of the invention, a combination of an immediate release form and a sustained release form of corticosteroids is administered (e.g., by single injection or as sequential injections) into an intra-articular space or into soft tissues to slow, arrest, reverse or otherwise inhibit structural damage to tissues associated with progressive disease such as, for example, the damage to cartilage associated with progression of osteoarthritis. The formulations and methods of embodiments of the invention can achieve immediate relief of the acute symptoms (e.g., pain and inflammation) of these diseases or conditions and additionally provide a sustained or long term therapy (e.g., slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease), while avoiding long term systemic side effects associated with corticosteroid administration, including HPA suppression.

In one aspect, a formulation is provided wherein a microparticle matrix (such as PLGA, PLA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the corticosteroid microparticle formulation provides at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days of a sustained, steady state release of the corticosteroid. In one aspect, a formulation is provided wherein a microparticle matrix (such as PLGA, PLA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the corticosteroid microparticle formulation provides at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days of a sustained, steady state release of the corticosteroid at a rate that does not adversely suppress the HPA axis.

The corticosteroid microparticle formulation retains sustained efficacy even after the corticosteroid is no longer resident at the site of administration, for example, in the intra-articular space, and/or after the corticosteroid is no longer detected in the systemic circulation. The corticosteroid microparticle formulation retains sustained efficacy even after the corticosteroid microparticle formulation is no longer resident at the site of administration, for example, in the intra-articular space, and/or the corticosteroid microparticle formulation is no longer detected in the systemic circulation. The corticosteroid microparticle formulation retains sustained efficacy even after the corticosteroid microparticle formulation ceases to release therapeutically effective amounts of corticosteroid. For example, in some embodiments, the corticosteroid released by the microparticle formulation retains efficacy for at least one week, at least two weeks, at least three weeks, at least four weeks, at least five weeks, at least six weeks, at least seven weeks, at least eight weeks, at least nine weeks, at least twelve weeks, or more than twelve-weeks post-administration. In some embodiments, the corticosteroid released by the microparticle formulation retains efficacy for a time period that is at least twice as long, at least three times as long, or more than three times as long as the residency period for the corticosteroid and/or the corticosteroid microparticle formulation. In some embodiments, the sustained, steady state release of corticosteroid will not adversely suppress the HPA axis.

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In some embodiments, a controlled or sustained-release formulation is provided wherein a microparticle matrix (such as PLGA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the formulation may or may not exhibit an initial rapid release, also referred to herein as an initial "burst" of the corticosteroid for a first length of time of between 0 and 14 days, for example, between the beginning of day 1 through the end of day 14, in addition to the sustained, steady state release of the corticosteroid for a second length of time of at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days. It should be noted that when corticosteroid levels are measured in vitro, an occasional initial burst of corticosteroid release from the microparticle formulation can be seen, but this initial burst may or may not be seen in vivo. In another embodiment, a controlled or sustained-release formulation is provided wherein a microparticle matrix (such as PLGA, hydrogels, hyaluronic acid, etc.) incorporates a corticosteroid, and the formulation may or may not exhibit an initial rapid release, also referred to herein as an initial "burst" of the corticosteroid for a first length of time of between 0 and 14 days, e.g., between the beginning of day 1 through the end of day 14, in addition to the sustained, steady state release of the corticosteroid for a second length of time of at least two weeks, preferably at least three weeks, including up to and beyond 30 days, or 60 days, or 90 days where the sustained, steady state release of corticosteroid is released at a rate that does not suppress the HPA axis at a level greater than 50% at day 14 post-administration. In some embodiments, the sustained, steady state release of corticosteroid will not adversely suppress the HPA axis, for example, the level of HPA axis suppression at or less than 35% by day 14 post-administration. In some embodiments, the sustained, steady state release of corticosteroid does not significantly suppress the HPA axis, for example, the level of HPA axis suppression is negligible and/or undetectable by day 14 post-injection. In some embodiments, the sustained, steady state release of corticosteroid does not significantly suppress the HPA axis, for example, the level of HPA axis suppression is negligible at all times post-injection. In some embodiments, the length of sustained release is between 21 days and 90 days. In some embodiments, the length of sustained release is between 21 days and 60 days. In some embodiments, the length of sustained release is between 14 days and 30 days. In some embodiments, the length of release of the initial "burst" component is between 0 and 10 days, for example between the beginning of day 1 through the end of day 10. In some embodiments, the length of release of the initial "burst" component is between 0 and 6 days, for example between the beginning of day 1 through the end of day 6. In some embodiments, the length of initial "burst," component is between 0 and 2 days, for example between the beginning of day 1 through the end of day 2. In some embodiments, the length of initial "burst" component is between 0 and 1 day, for example between the beginning of day 1 through the end of day 1.

The corticosteroid microparticle formulations provided herein can be used in combination with any of a variety of therapeutics, also referred to herein as "co-therapies." For example, the corticosteroid microparticle formulations can be used in combination with an immediate release corticosteroid solution or suspension, which provides high local exposures for between 1 day and 14 days following administration and which produce systemic exposures that may be associated with transient suppression of the HPA axis. For example, 40 mg of immediate release triamcinolone acetonide co-administered with the corticosteroid microparticle formulation in the intra-articular space would be

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expected to produce high local concentrations lasting for about 12 days. These high local concentrations would be associated with peak plasma concentration of triamcinolone acetonide of approximately 10 ng/ml on day 1, and over the course of the first 12 days of release of the triamcinolone acetonide from the intra-articular space would be associated with transient suppression of the HPA axis with a maximal effect of approximately 60% suppression of cortisol on day 1-2 (Derendorf et al., "Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration." *Clin Pharmacol Ther.* 39(3) (1986):313-7). By day 12, the contribution of the immediate release component to the plasma concentration would be small, less than 0.1 ng/ml, and the contribution to the intra articular concentration of the immediate release component would also be small. However at day 12 and beyond, the corticosteroid microparticle formulation would continue to release corticosteroid in the intra articular space at a rate that extends the duration of therapeutic effect and does not suppress the HPA axis. In some embodiments, the same corticosteroid is used in both the immediate release and sustained release components. In some embodiments, the immediate release component contains a corticosteroid that is different from that of the sustained release component. In some embodiments, the sustained, steady state release of corticosteroid will not adversely suppress the HPA axis. In some embodiments, the period of sustained release is between 21 days and 90 days. In some embodiments, the period of sustained release is between 21 days and 60 days. In some embodiments, the period of sustained release is between 14 days and 30 days. In some embodiments, the high local exposure attributable to the immediate release component lasts for between 1 day and 14 days. In some embodiments, the high local exposure attributable to the immediate release component lasts for between 1 day and 10 days. In some embodiments, the high local exposure attributable to the immediate release component lasts between 1 days and 8 days. In some embodiments, the high local exposure attributable to the immediate release component lasts between 1 days and 6 days. In some embodiments, the high local exposure attributable to the immediate release component lasts for between 1 day and 4 days.

Upon administration, the corticosteroid microparticle formulation may provide an initial release of corticosteroid at the site of administration, for example, in the intra-articular space and/or peri-articular space. Once the initial release of corticosteroid has subsided, the controlled or sustained release of the corticosteroid microparticle formulations continues to provide therapeutic (e.g., intra-articular and/or peri-articular) concentrations of corticosteroid to suppress inflammation, maintain analgesia, and/or slow, arrest or reverse structural damage to tissues for an additional period of therapy following administration (FIG. 1, top tracings). However, the systemic exposure associated with the sustained release component does not suppress the HPA axis (FIG. 1, bottom tracings). Thus, the invention includes therapies and formulations that may exhibit an initial release of corticosteroid followed by controlled or sustained release where the therapy comprises a period of therapy wherein the corticosteroid is released from the sustained release component and the plasma levels of the corticosteroid does not adversely suppress the HPA axis.

In some embodiments, the length of sustained release is between 21 days and 90 days. In some embodiments, the length of sustained release is between 21 days and 60 days. In some embodiments, the length of sustained release is between 14 days and 30 days. In some embodiments, the length of release of the immediate release form is between 1 day and 14

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days. In some embodiments, the length of release of the immediate release form is between 1 day and 10 days. In some embodiments, the length of release of the immediate release form is between 1 day and 8 days. In some embodiments, the length of release of the immediate release form is between 1 day and 6 days. In some embodiments, the length of release of the immediate release form is between 1 day and 4 days.

The invention provides populations of microparticles including a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid is between 22% to 28% of the microparticles.

The invention also provides controlled or sustained release preparation of a Class B corticosteroid that include a lactic acid-glycolic acid copolymer microparticle containing the Class B corticosteroid, wherein the Class B corticosteroid is between 22% to 28% of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention also provides formulations that include (a) controlled- or sustained-release microparticles comprising a Class B corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.3 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 80:20 to 60:40; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In some embodiments of these populations, preparations and/or formulations, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid from the range of about 80:20 to 60:40. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 75:25.

The invention also provides populations of microparticles including a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a mixed molecular weight lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid is between 12% to 28% of the microparticles. In some embodiments, the corticosteroid microparticle formulation includes a Class B corticosteroid and a microparticle made using 75:25 PLGA formulation with two PLGA polymers, one of low molecular weight and one of high molecular weight in a two to one ratio, respectively. The low molecular weight PLGA has a molecular weight of range of 15-35 kDa and an inherent viscosity range from 0.2 to 0.35 dL/g and the high molecular weight PLGA has a range of 70-95 kDa and an inherent viscosity range of 0.5 to 0.70 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 μ m, or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

The invention also provides populations of microparticles including a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid

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copolymer matrix containing 10-20% triblock (PEG-PLGA-PEG) having an inherent viscosity in the range from 0.6 to 0.8 dL/g, wherein the Class B corticosteroid is between 22% to 28% of the microparticles. In some embodiments, the corticosteroid microparticle formulation includes a Class B corticosteroid and a microparticle made using 75:25 PLGA formulation and containing 10-20% triblock (PEG-PLGA-PEG) having an inherent viscosity in the range from 0.6 to 0.8 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

These Class B corticosteroid microparticle formulations, preparations, and populations thereof, when administered to a patient, exhibit reduced undesirable side effects in patient, for example, undesirable effects on a patient's cartilage or other structural tissue, as compared to the administration, for example administration into the intra-articular space of a joint, of an equivalent amount of the Class B corticosteroid absent any microparticle or other type of incorporation, admixture, or encapsulation.

In some embodiments, the Class B corticosteroid is triamcinolone acetonide or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, the total dose of corticosteroid contained in the microparticles is in the range of 10-90 mg, where the Class B corticosteroid is between 12-28% of the microparticle, for example, between 22-28% of the microparticle (i.e., when the corticosteroid is 28% of the microparticle, the microparticle is in the range of 35.7-321.4 mgs, and so on for all values between 22-28% load dose, when the corticosteroid is 25% of the microparticle, the microparticle is in the range of 40-360 mgs, when the corticosteroid is 22% of the microparticle, the microparticle is in the range of 45.5-409.1 mgs, when the corticosteroid is 12% of the microparticle, the microparticle is in the range of 83.3-750 mgs, and so on for all values between 12-28% load dose). In some embodiments, the Class B corticosteroid contained in the microparticles is 12-28% of the microparticle, for example, between 22-28% of the microparticle and the total dose of corticosteroid is in a range selected from 10-80 mg, 10-70 mg, 10-60 mg, 10-50 mg, 10-40 mg, 10-30 mg, 10-20 mg, 20-90 mg, 20-80 mg, 20-70 mg, 20-60 mg, 20-50 mg, 20-40 mg, 20-30 mg, 30-90 mg, 30-80 mg, 30-70 mg, 30-60 mg, 30-50 mg, 30-40 mg, 40-90 mg, 40-80 mg, 40-70 mg, 40-60 mg, 40-50 mg, 50-90 mg, 50-80 mg, 50-70 mg, 50-60 mg, 60-90 mg, 60-80 mg, 60-70 mg, 70-90 mg, 70-80 mg, and 80-90 mg. In some embodiments, the Class B corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μ m to 100 μ m, for example, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or

formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes triamcinolone acetonide (TCA) and a microparticle made using 75:25 PLGA formulation having an inherent viscosity in the range from 0.3 to 0.5 dL/g and/or a molecular weight in the range of 40-70 kDa, for example between 50-60 kDa. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the TCA/75:25 PLGA microparticle formulations, the range of TCA load percentage is between 22-28%. In one embodiment, the load percentage of TCA in the microparticles is 25%.

The microparticles in the TCA PLGA microparticle formulations can be formulated using PLGA polymers having a range of molecular weights from 40 to 70 kDa, most preferably from 50 to 60 kDa and range of inherent viscosities from 0.5 to 0.5 dL/g, most preferably from 0.38 to 0.42 dL/g.

For the TCA/75:25 PLGA microparticle formulations, the total dose of corticosteroid contained in the microparticles is in the range of 10-90 mg, where TCA is between 22-28% of the microparticle (i.e., when TCA is 25% of the microparticle, the microparticle is in the range of 40-360 mgs, when TCA is 22% of the microparticle, the microparticle is in the range of 45.5-409.1 mgs, when TCA is 28% of the microparticle, the microparticle is in the range of 35.7-321.4 mgs, and so on for all values between 22-28% load dose). In some embodiments, total dose of corticosteroid contained in the microparticles is in a range selected from 10-80 mg, 10-70 mg, 10-60 mg, 10-50 mg, 10-40 mg, 10-30 mg, 10-20 mg, 20-90 mg, 20-80 mg, 20-70 mg, 20-60 mg, 20-50 mg, 20-40 mg, 20-30 mg, 30-90 mg, 30-80 mg, 30-70 mg, 30-60 mg, 30-50 mg, 30-40 mg, 40-90 mg, 40-80 mg, 40-70 mg, 40-60 mg, 40-50 mg, 50-90 mg, 50-80 mg, 50-70 mg, 50-60 mg, 60-90 mg, 60-80 mg, 60-70 mg, 70-90 mg, 70-80 mg, and 80-90 mg.

In some embodiments of the TCA/75:25 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes triamcinolone acetonide (TCA) and a microparticle made using 75:25 PLGA formulation and containing 10-20% triblock (PEG-PLGA-PEG) having an inherent viscosity in the range from 0.6 to 0.8 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The

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diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes triamcinolone acetonide (TCA) and a microparticle made using 75:25 PLGA formulation with two PLGA polymers, one of low molecular weight and one of high molecular weight in a two to one ratio, respectively. The low molecular weight PLGA has a molecular weight of range of 15-35 kDa and an inherent viscosity range from 0.2 to 0.35 dL/g and the high molecular weight PLGA has a range of 70-95 kDa and an inherent viscosity range of 0.5 to 0.70 dL/g. In these TCA/75:25 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

These TCA microparticle formulations, preparations, and populations thereof, when administered to a patient, exhibit reduced undesirable side effects in patient, for example, undesirable effects on a patient's cartilage or other structural tissue, as compared to the administration, for example administration into the intra-articular space of a joint, of an equivalent amount of TCA absent any microparticle or other type of incorporation, admixture, or encapsulation.

In another embodiment, the corticosteroid microparticle formulation includes a Class A, C, or D corticosteroid and a microparticle made using 50:50 PLGA formulation. For example, in some embodiments, the Class A corticosteroid is prednisolone. In some embodiments, the Class C corticosteroid is betamethasone. In some embodiments, the Class D corticosteroid is fluticasone or fluticasone propionate. In these Class A, C, or D corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 μ m, or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the Class A and/or Class C PLGA microparticle formulations, the range of corticosteroid load percentage is between 10-40%, for example, between 15%-30%. For the Class D PLGA microparticle formulations, the range of corticosteroid load percentage is between 8-20%.

The microparticles in the Class A, C or D PLGA microparticle formulations can be formulated using PLGA polymers having a range of inherent viscosities from 0.35 to 0.5 dL/g and approximated molecular weights from 40 kDa to 70 kDa.

These Class A, C or D corticosteroid microparticle formulations, preparations, and populations thereof, when administered to a patient, exhibit reduced undesirable side effects in patient, for example, undesirable effects on a patient's cartilage or other structural tissue, as compared to the administration, for example administration into the intra-articular space of a joint, of an equivalent amount of the Class A, C or D corticosteroid absent any microparticle or other type of incorporation, admixture, or encapsulation.

The invention provides populations of microparticles including a Class A corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsu-

lated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid is between 15% to 30% of the microparticles.

The invention also provides controlled or sustained release preparations of a Class A corticosteroid including a lactic acid-glycolic acid copolymer microparticle containing the Class A corticosteroid, wherein the Class A corticosteroid is between 10% to 40%, for example between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention provides formulations that include (a) controlled- or sustained-release microparticles including a Class A corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid is between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.35 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 60:40 to 45:55; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In some embodiments, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid in the range of about 60:40 to 45:55. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.

In some embodiments, the Class A corticosteroid is prednisolone or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, total dose of the Class A corticosteroid contained in the microparticles is in a range selected from 10-250 mg, where the Class A corticosteroid is between 10-40%, for example, between 15-30% of the microparticle (i.e., when the corticosteroid is 10% of the microparticle, the microparticle is in the range of 100-2500 mgs, when the corticosteroid is 15% of the microparticle, the microparticle is in the range of 66.7-1666.7 mgs, when the corticosteroid is 20% of the microparticle, the microparticle is in the range of 50-1250 mgs, when the corticosteroid is 25% of the microparticle, the microparticle is in the range of 40-1000 mgs, when the corticosteroid is 30% of the microparticle, the microparticle is in the range of 33.3-833.3 mgs, when the corticosteroid is 40% of the microparticle, the microparticle is in the range of 25-625 mgs and so on for all values between 10-40% load dose). For example, in some embodiments, the total dose of corticosteroid is in the range of 10-225 mg, 10-200 mg, 10-175 mg, 10-150 mg, 10-120 mg, 10-100 mg, 10-75 mg, 10-50 mg, 10-25 mg, 20-250 mg, 20-225 mg, 20-200 mg, 20-175 mg, 20-150 mg, 20-125 mg, 20-100 mg, 20-75 mg, 20-50 mg, 30-250 mg, 30-225 mg, 30-200 mg, 30-175 mg, 30-150 mg, 30-120 mg, 30-100 mg, 30-75 mg, 30-50 mg, 40-250 mg, 40-225 mg, 40-200 mg, 40-175 mg, 40-150 mg, 40-120 mg, 40-100 mg, 40-75 mg, 50-250 mg, 50-225 mg, 50-200 mg, 50-175 mg, 50-150 mg, 50-120 mg, 50-100 mg, 50-75 mg, 60-250 mg, 60-225 mg, 60-200 mg, 60-175 mg, 60-150 mg, 60-120 mg, 60-100 mg, 60-75 mg, 70-250 mg, 70-225 mg, 70-200 mg, 70-175 mg, 70-150 mg, 70-120 mg, 70-100 mg, 80-250 mg, 80-225 mg, 80-200 mg, 80-175 mg, 80-150 mg, 80-120 mg, 80-100 mg, 90-250 mg, 90-225 mg, 90-200 mg, 90-175 mg, 90-150 mg, or 90-120 mg. In some embodiments, the Class A corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μ m to 100 μ m, for example, the microparticles have a mean diameter in the range of 20-100

μM , 20-90 μM , 30-100 μM , 30-90 μM , or 10-90 μM . It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes prednisolone and a microparticle made using 50:50 PLGA formulation having a molecular weight in the range of 40 kDa to 70 kDa. In these prednisolone/50:50 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μM . In some embodiments, the microparticles have a mean diameter in the range of 20-100 μM , 20-90 μM , 30-100 μM , 30-90 μM , or 10-90 μM .

For the prednisolone/50:50 PLGA microparticle formulations, the range of prednisolone load percentage is between 10-40%, for example, between 15-30%.

In some embodiments of the prednisolone/50:50 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

The invention provides populations of microparticles including a Class C corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid is between 10% to 40% of the microparticles, for example between 15% to 30% of the microparticles.

The invention also provides controlled or sustained release preparations of a Class C corticosteroid including a lactic acid-glycolic acid copolymer microparticle containing the Class C corticosteroid, wherein the Class C corticosteroid is between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention provides formulations that include (a) controlled- or sustained-release microparticles having a Class C corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid is between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.35 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 60:40 to 45:55; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In one embodiment of these populations, preparations and/or formulations, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some

embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.

In some embodiments, the Class C corticosteroid is betamethasone or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, total dose of the Class C corticosteroid contained in the microparticles is in a range selected from 2-250 mg, where the Class C corticosteroid is between 10-40%, for example, between 15-30% of the microparticle (i.e., when the corticosteroid is 10% of the microparticle, the microparticle is in the range of 20-2500 mgs, when the corticosteroid is 15% of the microparticle, the microparticle is in the range of 13.3-1666.7 mgs, when the corticosteroid is 20% of the microparticle, the microparticle is in the range of 10-1250 mgs, when the corticosteroid is 25% of the microparticle, the microparticle is in the range of 8-1000 mgs, when the corticosteroid is 30% of the microparticle, the microparticle is in the range of 6.67-833.3 mgs, when the corticosteroid is 40% of the microparticle, the microparticle is in the range of 5-625 mgs and so on for all values between 10-40% load dose). For example, in some embodiments, the total dose of corticosteroid is in the range of 2-225 mg, 2-200 mg, 2-175 mg, 2-150 mg, 2-120 mg, 2-100 mg, 2-75 mg, 2-60 mg, 2-55 mg, 2-50 mg, 2-45 mg, 2-40 mg, 2-35 mg, 2-30 mg, 2-25 mg, 2-20 mg, 2-15 mg, 2-10 mg, 4-225 mg, 4-200 mg, 4-175 mg, 4-150 mg, 4-120 mg, 4-100 mg, 4-75 mg, 4-60 mg, 4-55 mg, 4-50 mg, 4-45 mg, 4-40 mg, 4-35 mg, 4-30 mg, 4-25 mg, 4-20 mg, 4-15 mg, 4-10 mg, 5-225 mg, 5-200 mg, 5-175 mg, 5-150 mg, 5-120 mg, 5-100 mg, 5-75 mg, 5-60 mg, 5-55 mg, 5-50 mg, 5-45 mg, 5-40 mg, 5-35 mg, 5-30 mg, 5-25 mg, 5-20 mg, 5-15 mg, 5-10 mg, 6-225 mg, 6-200 mg, 6-175 mg, 6-150 mg, 6-120 mg, 6-100 mg, 6-75 mg, 6-60 mg, 6-55 mg, 6-50 mg, 6-45 mg, 6-40 mg, 6-35 mg, 6-30 mg, 6-25 mg, 6-20 mg, 6-15 mg, 6-10 mg, 8-225 mg, 8-200 mg, 8-175 mg, 8-150 mg, 8-120 mg, 8-100 mg, 8-75 mg, 8-60 mg, 8-55 mg, 8-50 mg, 8-45 mg, 8-40 mg, 8-35 mg, 8-30 mg, 8-25 mg, 8-20 mg, 8-15 mg, 8-10 mg, 10-225 mg, 10-200 mg, 10-175 mg, 10-150 mg, 10-120 mg, 10-100 mg, 10-75 mg, 10-50 mg, 10-25 mg, 20-250 mg, 20-225 mg, 20-200 mg, 20-175 mg, 20-150 mg, 20-125 mg, 20-100 mg, 20-75 mg, 20-50 mg, 30-250 mg, 30-225 mg, 30-200 mg, 30-175 mg, 30-150 mg, 30-120 mg, 30-100 mg, 30-75 mg, 30-50 mg, 40-250 mg, 40-225 mg, 40-200 mg, 40-175 mg, 40-150 mg, 40-120 mg, 40-100 mg, 40-75 mg, 50-250 mg, 50-225 mg, 50-200 mg, 50-175 mg, 50-150 mg, 50-120 mg, 50-100 mg, 50-75 mg, 60-250 mg, 60-225 mg, 60-200 mg, 60-175 mg, 60-150 mg, 60-120 mg, 60-100 mg, 60-75 mg, 70-250 mg, 70-225 mg, 70-200 mg, 70-175 mg, 70-150 mg, 70-120 mg, 70-100 mg, 80-250 mg, 80-225 mg, 80-200 mg, 80-175 mg, 80-150 mg, 80-120 mg, 80-100 mg, 90-250 mg, 90-225 mg, 90-200 mg, 90-175 mg, 90-150 mg, or 90-120 mg. In some embodiments, the Class C corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μm to 100 μm , for example, the microparticles have a mean diameter in the range of 20-100 μM , 20-90 μM , 30-100 μM , 30-90 μM , or 10-90 μM . It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of

PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes betamethasone and a microparticle made using 50:50 PLGA formulation having a molecular weight in the range of 40 kDa to 70 kDa. In these betamethasone/50:50 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ M. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the betamethasone/50:50 PLGA microparticle formulations, the range of prednisolone load percentage is between 10-40%, for example, between 15-30%.

In some embodiments of the betamethasone/50:50 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

The invention provides populations of microparticles including a Class D corticosteroid or a pharmaceutically acceptable salt thereof incorporated in, admixed, encapsulated or otherwise associated with a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid is between 8% to 20% of the microparticles, for example, between 10% to 20% of the microparticles.

The invention also provides controlled or sustained release preparation of a Class D corticosteroid including a lactic acid-glycolic acid copolymer microparticle containing the Class D corticosteroid, wherein the Class D corticosteroid is between 8% to 20%, for example, between 10% to 20% of the microparticles of the lactic acid-glycolic acid copolymer microparticle matrix.

The invention provides formulations including (a) controlled- or sustained-release microparticles having a Class D corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid is between 8% to 20% of the microparticles, for example, between 10% to 20% of the microparticles, and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; (ii) an inherent viscosity in the range of 0.35 to 0.5 dL/g; (iii) a lactide:glycolide molar ratio of 60:40 to 45:55; and/or (iv) the lactic acid-glycolic acid copolymer is carboxylic acid endcapped.

In one embodiment of these populations, preparations and/or formulations, the copolymer is biodegradable. In some embodiments, the lactic acid-glycolic acid copolymer is a poly(lactic-co-glycolic) acid copolymer (PLGA). In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid from the range of about 60:40 to 45:55. In some embodiments, the lactic acid-glycolic acid copolymer has a molar ratio of lactic acid:glycolic acid of 50:50.

In some embodiments, the Class D corticosteroid is fluticasone propionate, fluticasone, or a commercially available chemical analogue or a pharmaceutically-acceptable salt thereof. In some embodiments, total dose of the Class D

corticosteroid contained in the microparticles is in a range selected from 1-250 mg, where the Class D corticosteroid is between 8-20% of the microparticle (i.e., when the corticosteroid is 8% of the microparticle, the microparticle is in the range of 12.5-3125 mgs, when the corticosteroid is 10% of the microparticle, the microparticle is in the range of 10-2500 mgs, when the corticosteroid is 15% of the microparticle, the microparticle is in the range of 6.67-1666.7 mgs, when the corticosteroid is 20% of the microparticle, the microparticle is in the range of 5-1250 mgs, and so on for all values between 10-20% load dose). For example, in some embodiments, the total dose of corticosteroid is in the range of 1-225 mg, 1-200 mg, 1-175 mg, 1-150 mg, 1-120 mg, 1-100 mg, 1-75 mg, 1-60 mg, 1-55 mg, 1-50 mg, 1-45 mg, 1-40 mg, 1-35 mg, 1-30 mg, 1-25 mg, 1-20 mg, 1-15 mg, 1-10 mg, 2-225 mg, 2-200 mg, 2-175 mg, 2-150 mg, 2-120 mg, 2-100 mg, 2-75 mg, 2-60 mg, 2-55 mg, 2-50 mg, 2-45 mg, 2-40 mg, 2-35 mg, 2-30 mg, 2-25 mg, 2-20 mg, 2-15 mg, 2-10 mg, 3-225 mg, 3-200 mg, 3-175 mg, 3-150 mg, 3-120 mg, 3-100 mg, 3-75 mg, 3-60 mg, 3-55 mg, 3-50 mg, 3-45 mg, 3-40 mg, 3-35 mg, 3-30 mg, 3-25 mg, 3-20 mg, 3-15 mg, 3-10 mg, 4-225 mg, 4-200 mg, 4-175 mg, 4-150 mg, 4-120 mg, 4-100 mg, 4-75 mg, 4-60 mg, 4-55 mg, 4-50 mg, 4-45 mg, 4-40 mg, 4-35 mg, 4-30 mg, 4-25 mg, 4-20 mg, 4-15 mg, 4-10 mg, 5-225 mg, 5-200 mg, 5-175 mg, 5-150 mg, 5-120 mg, 5-100 mg, 5-75 mg, 5-60 mg, 5-55 mg, 5-50 mg, 5-45 mg, 5-40 mg, 5-35 mg, 5-30 mg, 5-25 mg, 5-20 mg, 5-15 mg, 5-10 mg, 6-225 mg, 6-200 mg, 6-175 mg, 6-150 mg, 6-120 mg, 6-100 mg, 6-75 mg, 6-60 mg, 6-55 mg, 6-50 mg, 6-45 mg, 6-40 mg, 6-35 mg, 6-30 mg, 6-25 mg, 6-20 mg, 6-15 mg, 6-10 mg, 8-225 mg, 8-200 mg, 8-175 mg, 8-150 mg, 8-120 mg, 8-100 mg, 8-75 mg, 8-60 mg, 8-55 mg, 8-50 mg, 8-45 mg, 8-40 mg, 8-35 mg, 8-30 mg, 8-25 mg, 8-20 mg, 8-15 mg, 8-10 mg, 10-225 mg, 10-200 mg, 10-175 mg, 10-150 mg, 10-120 mg, 10-100 mg, 10-75 mg, 10-50 mg, 10-25 mg, 20-250 mg, 20-225 mg, 20-200 mg, 20-175 mg, 20-150 mg, 20-125 mg, 20-100 mg, 20-75 mg, 20-50 mg, 30-250 mg, 30-225 mg, 30-200 mg, 30-175 mg, 30-150 mg, 30-120 mg, 30-100 mg, 30-75 mg, 30-50 mg, 40-250 mg, 40-225 mg, 40-200 mg, 40-175 mg, 40-150 mg, 40-120 mg, 40-100 mg, 40-75 mg, 50-250 mg, 50-225 mg, 50-200 mg, 50-175 mg, 50-150 mg, 50-120 mg, 50-100 mg, 50-75 mg, 60-250 mg, 60-225 mg, 60-200 mg, 60-175 mg, 60-150 mg, 60-120 mg, 60-100 mg, 60-75 mg, 70-250 mg, 70-225 mg, 70-200 mg, 70-175 mg, 70-150 mg, 70-120 mg, 70-100 mg, 80-250 mg, 80-225 mg, 80-200 mg, 80-175 mg, 80-150 mg, 80-120 mg, 80-100 mg, 90-250 mg, 90-225 mg, 90-200 mg, 90-175 mg, 90-150 mg, or 90-120 mg. In some embodiments, the Class D corticosteroid is released for between 14 days and 90 days.

In some embodiments, the microparticles have a mean diameter of between 10 μ m to 100 μ m, for example, the microparticles have a mean diameter in the range of 20-100 μ M, 20-90 μ M, 30-100 μ M, 30-90 μ M, or 10-90 μ M. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

In some embodiments, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

In one embodiment of these populations, preparations and/or formulations, the corticosteroid microparticle formulation includes fluticasone propionate or fluticasone, and a micro-

particle made using 50:50 PLGA formulation having a molecular weight in the range of 40 kDa to 70 kDa. In these fluticasone or fluticasone propionate/50:50 PLGA corticosteroid microparticle formulations, the microparticles have a mean diameter in the range of 10-100 μ m. In some embodiments, the microparticles have a mean diameter in the range of 20-100 μ m, 20-90 μ m, 30-100 μ m, 30-90 or 10-90 μ m. It is understood that these ranges refer to the mean diameter of all microparticles in a given population. The diameter of any given individual microparticle could be within a standard deviation above or below the mean diameter.

For the fluticasone or fluticasone propionate/50:50 PLGA microparticle formulations, the range of prednisolone load percentage is between 10-20%.

In some embodiments of the fluticasone or fluticasone propionate/50:50 PLGA microparticle formulations, the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle. In some embodiments of the microparticles that include a PEG moiety, the populations, preparations and/or formulations of the invention do not require the presence of PEG to exhibit the desired corticosteroid sustained release kinetics and bioavailability profile.

These embodiments of corticosteroid microparticle formulations have been selected because the combination of class of corticosteroid, type of microparticle, molecular weight of polymers used to create the microparticles lactide:glycolide molar ratio, and/or load percentage of the corticosteroid exhibit the desired release kinetics. These embodiments also exhibit the desired release kinetics with minimal prolonged HPA axis suppression.

The invention provides methods of treating pain or inflammation in a patient comprising administering to said patient a therapeutically effective amount of a population of microparticles selected from the following populations: (i) a population of microparticles comprising a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles; (ii) a population of microparticles comprising a Class A corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles; (iii) a population of microparticles comprising a Class C corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid comprises between 15% to 30% of the microparticles; and (iv) a population of microparticles comprising a Class D corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles. In some embodiments, the population of microparticles releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). In some embodiments, the population of microparticles releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-administration. In some embodiments, the population of microparticles releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration. In some embodiments, the population of microparticles releases the corticosteroid in a controlled or

sustained release manner such that the levels of cortisol suppression are negligible at any time post-administration.

The invention provides methods of treating pain or inflammation in a patient comprising administering to said patient a therapeutically effective amount of a controlled or sustained release preparation selected from the following preparations: (i) a controlled or sustained release preparation of a Class B corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class B corticosteroid, wherein the Class B corticosteroid comprises between 22% to 28% of the lactic acid-glycolic acid copolymer microparticle matrix; (ii) a controlled or sustained release preparation of a Class A corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class A corticosteroid, wherein the Class A corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; (iii) a controlled or sustained release preparation of a Class C corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class C corticosteroid, wherein the Class C corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; and (iv) a controlled or sustained release preparation of a Class D corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class D corticosteroid, wherein the Class D corticosteroid comprises between 8% to 20% of the lactic acid-glycolic acid copolymer microparticle matrix. In some embodiments, the controlled or sustained release preparation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). In some embodiments, the controlled or sustained release preparation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-administration. In some embodiments, the controlled or sustained release preparation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration. In some embodiments, the controlled or sustained release preparation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible at any time post-administration.

The invention provides methods of treating pain or inflammation in a patient comprising administering to said patient a therapeutically effective amount of a formulation selected from the following preparations: (i) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class B corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.5 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 80:20 to 60:40; (ii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class A corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 45:55; (iii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class C corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the

Class C corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 45:55; and (iv) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class D corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 45:55. In some embodiments, the formulation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). In some embodiments, the formulation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-administration, for example post-administration. In some embodiments, the formulation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-administration. In some embodiments, the formulation releases the corticosteroid in a controlled or sustained release manner such that the levels of cortisol suppression are negligible at any time post-administration.

In some embodiments, the population of microparticles, the controlled or sustained release preparation or formulation is administered as one or more intra-articular injections. In some embodiments, the patient has osteoarthritis, rheumatoid arthritis, acute gouty arthritis, and synovitis. In some embodiments, the patient has acute bursitis, sub-acute bursitis, acute nonspecific tenosynovitis, or epicondylitis.

In one aspect, a method of treating pain and/or inflammation in a joint of a patient is provided that includes administering intra-articularly (e.g., by one or more injections) to a patient with joint disease (e.g., osteoarthritis or rheumatoid arthritis) a formulation that contains one or more corticosteroids, such as those formulations described herein. Therapeutically effective amounts of the one or more corticosteroids are released for a period of time at a rate that does not suppress (e.g., adversely and/or measurably) the HPA axis.

In another aspect, a method of treating pain and/or inflammation in a joint of a patient is provided that includes administering intra-articularly (e.g., by one or more injections) a therapeutically effective amount of one or more corticosteroids in a formulation to a patient with joint disease (e.g., osteoarthritis or rheumatoid arthritis). The formulation has a sustained release microparticle formulation that may or may not release detectable levels of corticosteroid for a length of time following administration and that releases a detectable amount of corticosteroid(s) following administration, where the rate of corticosteroid release from the sustained release microparticle formulation does not adversely suppress the HPA axis. In some embodiments, corticosteroid released from the sustained release microparticle formulation will not measurably suppress the HPA axis.

According to certain embodiments of the foregoing methods, the formulation comprises a population of biodegradable polymer microparticles that contain the corticosteroids. In some embodiments, the corticosteroids are 2% to 75% (w/w) of the microparticles, preferably about 5% to 50% (w/w) of the microparticles, and more preferably 5% to 40% or 10% to 30% (w/w) of the microparticles. In some embodiments, the

microparticles have a mass mean diameter of between 10 μ m to 100 μ m. In some embodiments, the microparticles are formed from a hydrogel, hyaluronic acid, PLA or PLGA. For example, the microparticles are formed from PLGA with a lactide to glycolide co-polymer ratio of about 45:55 to about 80:20. In some embodiments, the corticosteroid is betamethasone, dexamethasone, triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, methylprednisolone, budesonide, mometasone, ciclesonide, fluticasone, salts thereof, esters thereof or combinations thereof.

In yet another aspect, a composition is provided that includes a population of biodegradable polymer microparticles that contain corticosteroid(s). For example, the corticosteroid is betamethasone, dexamethasone, triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, methylprednisolone, budesonide, mometasone, ciclesonide, fluticasone, salts thereof, esters thereof or combinations thereof. When the composition is administered intra-articularly (e.g., by one or more injections), a therapeutically effective amount of corticosteroid(s) is released for a period of time at a rate that does not suppress the HPA axis. In some embodiments, the corticosteroid(s) released will not adversely suppress the HPA axis. In some embodiments, the corticosteroid(s) released will not measurably suppress the HPA axis.

In yet a further aspect, a composition is provided that includes a population of biodegradable polymer microparticles that contain corticosteroid(s). For example, the corticosteroid is betamethasone, dexamethasone, triamcinolone acetonide, triamcinolone hexacetonide, prednisolone, methylprednisolone, budesonide, mometasone, ciclesonide, fluticasone, salts thereof, esters thereof or combinations thereof. When the composition is administered intra-articularly (e.g., by one or more injections), therapeutically effective amounts of corticosteroid(s) are released following administration from a first component for a first length of time and from a sustained release component for a second length of time. Furthermore, the rate of corticosteroid(s) released from the sustained release component does not suppress the HPA axis. In some embodiments, the corticosteroid(s) released from the sustained release component during the second length of time will not adversely suppress the HPA axis. In some embodiments, the corticosteroid(s) released from the sustained release component during the second length of time will not measurably suppress the HPA axis. In some embodiments, the first component comprises a corticosteroid containing solution or suspension. In some embodiments, the first component contains a corticosteroid that is different from that of the sustained release component. In other embodiments, the same corticosteroid is used in both the first and sustained release components.

According to certain embodiments of the foregoing compositions, the corticosteroids are 2% to 75% (w/w) of the microparticles, preferably about 5% to 50% (w/w) of the microparticles, and more preferably 5% to 40% (w/w) of the microparticles. In some embodiments, the microparticles have a mass mean diameter of between 10 μ m to 100 μ m. In some embodiments, the microparticles are formed from a hydrogel, hyaluronic acid, PLA or PLGA. For example, the microparticles are formed from PLGA with a lactide to glycolide co-polymer ratio of about 45:55 to about 80:20. In some embodiments, the compositions further comprise a corticosteroid containing solution or suspension. In some embodiments, the corticosteroid containing solution or suspension contains a corticosteroid that is different from that found in the microparticles.

The invention also provides methods of slowing, arresting or reversing progressive structural tissue damage associated

with chronic inflammatory disease in a patient comprising administering to said patient a therapeutically effective amount of a population of microparticles selected from the following populations: (i) a population of microparticles comprising a Class B corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles; (ii) a population of microparticles comprising a Class A corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles; (iii) a population of microparticles comprising a Class C corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid comprises between 15% to 30% of the microparticles; and (iv) a population of microparticles comprising a Class D corticosteroid or a pharmaceutically acceptable salt thereof incorporated in a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles. In some embodiments, the population of microparticles releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

The invention also provides methods of slowing, arresting or reversing progressive structural tissue damage associated with chronic inflammatory disease in a patient comprising administering to said patient a therapeutically effective amount of a controlled or sustained release preparation selected from the following preparations: (i) a controlled or sustained release preparation of a Class B corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class B corticosteroid, wherein the Class B corticosteroid comprises between 22% to 28% of the lactic acid-glycolic acid copolymer microparticle matrix; (ii) a controlled or sustained release preparation of a Class A corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class A corticosteroid, wherein the Class A corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; (iii) a controlled or sustained release preparation of a Class C corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class C corticosteroid, wherein the Class C corticosteroid comprises between 15% to 30% of the lactic acid-glycolic acid copolymer microparticle matrix; and (iv) a controlled or sustained release preparation of a Class D corticosteroid comprising a lactic acid-glycolic acid copolymer microparticle containing the Class D corticosteroid, wherein the Class D corticosteroid comprises between 8% to 20% of the lactic acid-glycolic acid copolymer microparticle matrix. In some embodiments, the controlled or sustained release preparation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

The invention also provides methods of slowing, arresting or reversing progressive structural tissue damage associated with chronic inflammatory disease in a patient comprising administering to said patient a therapeutically effective amount of a formulation selected from the following preparations: (i) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class B corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class B corticosteroid comprises between 22% to 28% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to

70 kDa; (2) an inherent viscosity in the range of 0.3 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 80:20 to 60:40; (ii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class A corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class A corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 50:50; (iii) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class C corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class C corticosteroid comprises between 15% to 30% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 50:50; and (iv) a formulation comprising (a) controlled- or sustained-release microparticles comprising a Class D corticosteroid and a lactic acid-glycolic acid copolymer matrix, wherein the Class D corticosteroid comprises between 8% to 20% of the microparticles and wherein the lactic acid-glycolic acid copolymer has one of more of the following characteristics: (1) a molecular weight in the range of about 40 to 70 kDa; (2) an inherent viscosity in the range of 0.35 to 0.5 dL/g; or (3) a lactide:glycolide molar ratio of 60:40 to 50:50. In some embodiments, the formulation releases the corticosteroid for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

In some embodiments, the population of microparticles, the controlled or sustained release preparation or formulation is administered as one or more intra-articular injections. In some embodiments, the patient has osteoarthritis, rheumatoid arthritis, acute gouty arthritis, and synovitis. In some embodiments, the patient has acute bursitis, sub-acute bursitis, acute nonspecific tenosynovitis, or epicondylitis.

The invention also provides methods to slow, arrest, reverse or otherwise inhibit progressive structural tissue damage associated with chronic inflammatory disease, for example, damage to cartilage associated with osteoarthritis. In one embodiment, the method includes the administration to a patient, for example local administration, of a therapeutically effective amount of one or more corticosteroids in a formulation, wherein the formulation releases the corticosteroid(s) for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis). The methods to assess the effect of corticosteroid formulations on disease progression include controlled clinical studies that assess clinical end points and for employ imaging technologies such as, for example Magnetic Resonance Imaging (MRI), to determine effects on the structure in chronically inflamed tissues, for example the effects on cartilage volume and other articular and peri-articular structures in osteoarthritis and rheumatoid arthritis. (See e.g., Eckstein F, et al. "Magnetic resonance imaging (MRI) of articular cartilage in knee osteoarthritis (OA): morphological assessment." *Osteoarthritis Cartilage* 14 Suppl A (2006): A46-75; Lo G H, et al. "Bone marrow lesions in the knee are associated with increased local bone density." *Arthritis Rheum* 52 (2005): 2814-21; and Lo G H, et al. "The ratio of medial to lateral tibial plateau bone mineral density and compartment-specific tibiofemoral osteoarthritis." *Osteoarthritis Cartilage* 14 (2006): 984-90 the contents of each of which are hereby incorporated by reference in their entirety.) The corticoster-

oid microparticle formulations provided herein appear to exhibit little to no negative effects, e.g., structural tissue damage, and from preliminary data and studies described in the Examples below, these corticosteroid microparticle formulations appear to have a positive effect, e.g., slowing, arresting or reversing structural tissue damage.

The invention also provides methods of treating pain and/or inflammation of a patient by administering to the patient a therapeutically effective amount of one or more corticosteroids in a formulation, wherein the formulation releases the corticosteroid(s) for at least 14 days at a rate that does not adversely suppress the hypothalamic-pituitary-adrenal axis (HPA axis).

The invention also provides methods of manufacturing the corticosteroid microparticle formulations. The microparticle formulations provided herein can be manufactured using any of a variety of suitable methods.

For the Class B corticosteroid microparticle formulations, in some embodiments, the microparticles are manufactured as described in the Examples provided below. For the Class B corticosteroid microparticle formulations, in some embodiments, the microparticles are manufactured as described in U.S. Pat. No. 7,261,529 and U.S. Pat. No. 7,758,778, the contents of each of which are hereby incorporated by reference in their entirety. For example, the microparticles are manufactured using a solvent evaporation process wherein the Class B corticosteroid is dispersed in a lactic acid-glycolic acid copolymer organic solution and the mixture is treated to remove the solvent from the mixture, thereby producing microparticles.

In some embodiments, the solvent evaporation process utilizes a spray drying or fluid bed apparatus to remove the solvent and produce microparticles. In some embodiments, the solvent evaporation process utilizes a spinning disk. For example, the spinning disk is the spinning disk as described in U.S. Pat. No. 7,261,529 and U.S. Pat. No. 7,758,778.

For the Class B corticosteroid microparticle formulations, in some embodiments where the Class B corticosteroid is TCA, the microparticles are manufactured using a solid in oil in water emulsion process wherein TCA is dispersed in a lactic acid-glycolic acid copolymer organic solution and added to an aqueous solvent to produce microparticles.

For the Class A, C and/or D corticosteroid microparticle formulations, in some embodiments, the microparticles are manufactured as described in the Examples provided below. For Class A, C and/or D corticosteroid formulations, in some embodiments, the microparticles are manufactured as described in PCT Publication No. WO 95/13799, the contents of which are hereby incorporated by reference in their entirety. For example, the microparticles are manufactured using a solid in oil in water emulsion process wherein the Class A corticosteroid, Class C corticosteroid and/or Class D corticosteroid is dispersed in a lactic acid-glycolic acid copolymer organic solution and added to an aqueous solvent to produce microparticles.

It is contemplated that whenever appropriate, any embodiment of the present invention can be combined with one or more other embodiments of the present invention, even though the embodiments are described under different aspects of the present invention.

BRIEF DESCRIPTION OF THE FIGURES

FIG. 1 is a graph depicting the intra-articular concentrations (top solid line) and the systemic concentrations (bottom solid line) of the glucocorticoid administered according to certain embodiments of the present invention following intra-

articular injection. The systemic glucocorticoid concentration associated with clinically significant suppression of the HPA axis is shown as the bottom dotted line. The top dotted line represents the minimal intra-articular concentration required to maintain efficacy (defined as relief of pain and inflammation, or slowing, arrest, or reversal of structural damage to tissues caused by inflammatory diseases. Sustained release of the corticosteroid provides sufficient intra-articular concentrations to maintain efficacy in the longer term, and has transient, clinically insignificant effect on the HPA axis.

FIG. 2 is a graph depicting the change in sensitivity over time to suppression of endogenous cortisol production (EC_{50} (ng/mL) vs. time) for triamcinolone acetone 40 mg given by intra-articular administration.

FIG. 3 is a graph depicting the change in sensitivity over time to suppression of endogenous cortisol production (EC_{50} (ng/mL) vs. time) for various corticosteroids administered as a single, intra-articular injection in the listed dose.

FIG. 4 is a graph depicting plasma levels of endogenous cortisol over time, without (Column 1) adjustment for a change in the sensitivity of the HPA axis after intra-articular corticosteroids and with (Column 2) adjustment for a change in the sensitivity of the HPA axis after intra-articular corticosteroids. These data demonstrate that the sensitivity of the HPA axis varies with corticosteroid, dose, and time with clinically important implications for the selection of doses for sustained delivery into an intra-articular space.

FIG. 5 is a graph depicting the cumulative percent release of a nominal 25% (w/w) triamcinolone acetone in PLGA 75:25 microparticles.

FIG. 6 is a graph depicting the calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 25% TCA PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 7 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 25% TCA PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 8 is a graph depicting cumulative percent release of a second preparation of nominal 25% triamcinolone acetone in PLGA 75:25 microparticles using an alternate preparation.

FIG. 9 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using a second preparation of nominal 25% TCA PLGA 75:25 microparticles made by an alternate preparation. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 10 is a graph depicting: calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using a second preparation of nominal 25% TCA PLGA 75:25 microparticles made by an alternate preparation. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 11 is a graph depicting cumulative percent release of nominal 25% triamcinolone acetone in 5% PEG 1450/PLGA 75:25 microparticles.

FIG. 12 is a graph depicting cumulative percent release of nominal 25% triamcinolone acetonide in 10% PEG 3350/PLGA 75:25 microparticles.

FIG. 13 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 25% TCA 5% PEG 1450/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 14 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 25% TCA 10% PEG 3350/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 15 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 25% TCA 5% PEG 1450/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 16 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 25% TCA 10% PEG 3350/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 17 is a graph depicting cumulative percent triamcinolone acetonide release of nominal 40%, 25% 20%, 15% and 10% TCA containing PLGA 75:25 microparticles.

FIG. 18 is a graph depicting cumulative percent release of nominal 25% TCA PLGA 75:25 (29 kDa) and PLGA 75:25 (54 kDa) containing microparticles.

FIG. 19 is a graph depicting cumulative percent release of triamcinolone acetonide in PLGA 50:50 microparticle formulations.

FIG. 20 is a graph depicting cumulative percent release of nominal 28.6% triamcinolone acetonide in PLGA 75:25 plus Triblock microparticle formulations.

FIG. 21 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% TCA 10% Triblock/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 22 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% TCA 20% Triblock/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 23 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% TCA 10% Triblock/PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 24 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% TCA 20% Triblock/PLGA 75:25

microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 25 is a graph depicting cumulative percent release of nominal 16.7% triamcinolone acetonide in mixed molecular weight PLGA 75:25 microparticle formulations.

FIG. 26 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 16.7% TCA mixed molecular weight PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 27 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 16.7% TCA mixed molecular weight PLGA 75:25 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 28 is a graph depicting cumulative percent release of nominal 28.6% triamcinolone acetonide in various polymer microparticle formulations.

FIG. 29 is a graph depicting cumulative percent release of nominal 28.6% Prednisolone in PLGA 50:50 microparticle formulation.

FIG. 30 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% PRED PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 31 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% PRED PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 32 is a graph depicting cumulative percent release of nominal 28.6% Betamethasone PLGA 50:50 microparticle formulation.

FIG. 33 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 28.6% BETA PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 34 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% BETA PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 35 is a graph depicting cumulative percent release of nominal 16.7% Fluticasone Propionate PLGA 50:50 microparticle formulation.

FIG. 36 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression using nominal 16.7% FLUT PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol

inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 37 is a graph depicting calculated human dose that does not affect the HPA axis, less than 35% cortisol suppression using nominal 16.7% FLUT PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIG. 38 is a graph depicting cumulative percent release of various Fluticasone Propionate PLGA microparticle formulations.

FIG. 39 is a graph depicting cumulative percent release of nominal 28.6% DEX PLGA 50:50 microparticle formulation.

FIG. 40 is a graph depicting calculated human dose to achieve transient cortisol suppression and within 14 days achieve less than 35% cortisol suppression and does not affect the HPA axis, less than 35% cortisol suppression using nominal 28.6% DEX PLGA 50:50 microparticles. The dotted lines represent, from top to bottom of the graph, 50% cortisol inhibition dose, 40% cortisol inhibition dose, 35% cortisol inhibition dose and 5% cortisol inhibition dose.

FIGS. 41A-41D are a series of graphs depicting the mean concentration-time profiles of various doses of TCA IR and FX006 in rat plasma following single intra-articular doses. A microparticle formulation of TCA in 75:25 PLGA formulation microparticles, referred to as FX006, dosed at 1.125 mg resulted in a very slow absorption of TCA in the systemic circulation and a markedly lower C_{max} as compared to TCA IR. Concentrations for the first 72 hr are presented in FIGS. 41C and 41D on a larger time scale.

FIG. 42 is a graph depicting corticosteroid inhibition and recovery with TCA IR (immediate release) and FX006 (microparticle formulation) in rats.

FIG. 43 is a graph depicting the pharmacokinetic/pharmacodynamic (PK/PD) relationship of systemic TCA levels and corticosterone inhibition.

FIGS. 44A-44C are a series of graphs depicting the gait analysis scores, an indicator of pain, in rats injected with doses of either immediate release triamcinolone acetonide (TCA IR) or TCA microparticles (FX006) in a model of osteoarthritis. In FIG. 44A, FX006 at 0.28, 0.12 and 0.03 mg (TCA doses) is expressed as TCA concentrations of the dosing formulation (4.67, 2 and 0.5 mg/ml). In FIG. 44B, FX006 at 0.28 mg (TCA dose) is expressed as TCA concentrations of the dosing formulation (4.67 mg/ml). Similarly, TCA IR at 0.03 mg is expressed as triamcinolone at 0.5 mg/ml. In FIG. 44C, FX006 at 0.28, 0.12 and 0.03 mg (TCA doses) is expressed as TCA concentrations of the dosing formulation (4.67, 2 and 0.5 mg/ml). Similarly, TCA IR at 0.06 and 0.03 mg is expressed as triamcinolone at 1 and 0.5 mg/ml.

FIG. 45 is a graph depicting peak pain response following repeated reactivations of arthritis in the right knee. All treatments were administered as a single IA dose in the right knee on Day 0.

FIG. 46 is a graph depicting the time course of corticosterone recovery for various groups in the rat study in a model of osteoarthritis.

FIGS. 47A-47B are a series of graphs depicting the plasma TCA concentration-time data for various groups in the rat study in a model of osteoarthritis. Only the groups that received injections of TCA microparticles (FX006 groups) are shown in FIG. 47B on an expanded scale.

FIG. 48 is a graph depicting the end-of-study histopathology scores for various treatment groups in the rat study in a model of osteoarthritis.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides compositions and methods for the treatment of pain and inflammation using corticosteroids. The compositions and methods provided herein use one or more corticosteroids in a microparticle formulation. The corticosteroid microparticle formulations provided herein are effective at treating pain and/or inflammation with minimal prolonged suppression of the HPA axis and/or other long term side effects of corticosteroid administration. The corticosteroid microparticle formulations provided herein are effective in slowing, arresting, reversing or otherwise inhibiting structural damage to tissues associated with progressive disease with minimal prolonged suppression of the HPA axis and/or other long term side effects of corticosteroid administration. The corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a sustained release manner such that the levels of cortisol suppression are at or below 35% by day 14 post-injection. In some embodiments, the corticosteroid microparticle formulations provided herein deliver the corticosteroid in a dose and in a controlled or sustained release manner such that the levels of cortisol suppression are negligible and/or undetectable by 14 post-injection. Thus, the corticosteroid microparticle formulations in these embodiments are effective in the absence of any significant HPA axis suppression. Administration of the corticosteroid microparticle formulations provided herein can result in an initial "burst" of HPA axis suppression, for example, within the first few days, within the first two days and/or within the first 24 hours post-injection, but by day 14 post-injection, suppression of the HPA axis is less than 35%.

The use of microparticles to administer corticosteroids is known (See, e.g., U.S. Patent Application Publication. No. 20080317805). In addition, corticosteroids are known to be useful for the symptomatic treatment of inflammation and pain. New data also suggest that synovitis may be associated with the structural damage, for example, the deterioration of cartilage and other peri-articular associated with the progression of osteoarthritis and rheumatoid arthritis. (See e.g., Hill C L, et al. "Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis." *Ann Rheum Dis* 66 (2007):1599-603; van den Berg W B, et al. "Synovial mediators of cartilage damage and repair in osteoarthritis." In: Brandt K D, Doherty M, Lohmander L S, eds. *Osteoarthritis*. Second ed. Oxford: Oxford University Press (2003):147-55; Ayral X, et al. "Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis—results of a 1 year longitudinal arthroscopic study in 422 patients." *Osteoarthritis Cartilage* 13 (2005):361-7; and Kirwan J R, et al. "Effects of glucocorticoids on radiological progression in rheumatoid arthritis." *Cochrane Database Syst Rev* 2007:CD006356).

The administration of corticosteroids, particularly for extended periods of time, can have a number of unwanted side effects. The HPA axis, the interdependent feedback mechanism between the hypothalamus, the pituitary gland and the adrenal cortex, may be suppressed by the administration of corticosteroids, leading to a variety of unwanted side effects. The extent of HPA axis suppression, and related inhibition of endogenous cortisol production, has been attributed to the potency of the corticosteroid, the dose, systemic concentration, protein binding, rate of elimination (Meibohm et al. "Mechanism-based PK/PD model for the lymphocytopenia induced by endogenous and exogenous corticosteroids." *Int J Clin Pharmacol Ther*. 37(8) (1999):367-76) and, for one corticosteroid, a change in sensitivity of the HPA axis (Derendorf et al. "Clinical PK/PD modelling as a tool in drug develop-

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ment of corticosteroids." *Int J Clin Pharmacol Ther.* 35(10) 1997: 481-8). Furthermore, intra-articular doses of corticosteroids associated with only limited anti-inflammatory and short-term analgesic benefit (Hepper et al. "The efficacy and duration of intra-articular corticosteroid injection for knee osteoarthritis: a systematic review of level I studies." *J Am Acad Orthop Surg.* 17(10) 2009: 638-46) have been associated with HPA axis suppression (Habib, "Systemic effects of intra-articular corticosteroids." *Clin Rheumatol.* 28(7) (2009): 749-56).

The changes in sensitivity to corticosteroid effects over time should alter clinical steroid dosing, but prior to the instant invention, this has not been understood.

The details of one or more embodiments of the invention are set forth in the accompanying description below. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. In the case of conflict, the present Specification will control.

DEFINITIONS

The terms below have the following meanings unless indicated otherwise.

An amount of a corticosteroid that does not "suppress the hypothalamic-pituitary-adrenal axis (HPA axis)" refers to the amount of the sustained release corticosteroid delivered locally to relieve pain due to inflammation, which provides a systemic concentration that will not have a clinically significant effect or "adverse effect" on the HPA axis. Suppression of the HPA axis is generally manifested by a reduction in endogenous glucocorticoid production. It is useful to consider both basal and augmented production of endogenous glucocorticoids. Under ordinary, "unstressed" conditions, glucocorticoid production occurs at a normal, basal level. There is some natural variation of production during the course of the 24-hour day. Under extraordinary, "stressed" conditions associated with, e.g., infection or trauma and the like, augmented endogenous production of glucocorticoids occurs. Endogenous cortisol production may be determined by measuring glucocorticoid concentrations in plasma, saliva, urine or by any other means known in the art. It is known that systemic concentrations of corticosteroids can suppress the HPA axis. For example, on day 3 after an intra-articular injection of 20 mg triamcinolone hexacetonide plasma levels, of approximately 3-4 ng/mL have been observed. These resulted in a transient but highly statistically significant 75% HPA-axis suppression (Derendorf et al., "Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration." *Clin Pharmacol Ther.* 39(3) (1986):313-7) which, however, does not necessarily portend complete HPA failure (Habib, "Systemic effects of intra-articular corticosteroids." *Clin Rheumatol* 28 (2009): 749-756, see p752 col. 1, para 2, final sentence). While such transient suppression is generally considered to be acceptable without clinically significant effect, more persistent suppression, i.e., weeks, would be deemed clinically detrimental. In embodiments of the present invention, administration of the formulation may result in a clinically acceptable HPA suppression, particularly during the initial release

period of the therapy. In some embodiments of the present invention, administration of the formulation will not result in any significant level of HPA suppression, including no detectable HPA suppression, particularly during the initial release period of the therapy. During the subsequent or sustained release period of the therapy, additional corticosteroid may be released into the plasma. However, the plasma levels during this period will generally be less than those during the initial release period, if any corticosteroid release occurs, and will not be associated with HPA axis suppression. Further, the adverse events associated with exogenous corticosteroid administration, e.g., hyperglycemia, hypertension, altered mood, etc. will generally not be observed. Preferably, the number of clinical adverse events during this period will not substantially exceed the number achieved by an immediate release formulation alone or by KENALOG™ or its bioequivalent and will, preferably, be fewer than during the prior, initial release period of the therapy, if any corticosteroid release occurs. Alternatively, one can determine the suppression of the formulation on HPA by measuring endogenous cortisol production. Thus, the formulation can be considered as avoiding clinically significant (or adverse) suppression of the HPA axis where the endogenous cortisol level is substantially the same in the steady state between a patient population receiving a therapeutically beneficial amount of an immediate release formulation and those receiving a therapeutically beneficial amount of a sustained release formulation. Such a formulation would be deemed to have no clinically significant effect on the HPA axis. Alternatively or additionally, a small but measurable reduction in steady-state glucocorticoid production can result from the formulation during the sustained release period of the therapy with adequate preservation of the augmented, stress response needed during infection or trauma can be deemed a clinically insignificant suppression of the HPA axis. Endogenous glucocorticoid production may be assessed by administering various doses of adrenocorticotropin hormone or by other tests known to those skilled in the art. Embodiments of the current invention provide for controlling the release of corticosteroid, as may be desired, to achieve either no measurable effect on endogenous glucocorticoid production or a target, or a measurable effect that is, however, without adverse clinical consequence. In this regard, it has been found that intra-articular doses of corticosteroids that suppress cortisol production by 20-35%, and sometimes more, provide very useful sustained anti-inflammatory and analgesic activity. These benefits are achieved without acute risks of hypoadrenalism and without excessive risks, after sustained intra-articular dosing, of developing an adrenal unresponsiveness in times of stress or of developing frank adrenal failure.

As shown further below, the studies presented herein have demonstrated that the HPA axis sensitivity appears to diminish with time, steroid, and dose. In this regard, it has been determined that standard doses of familiar corticosteroids, when examined from the viewpoint of steady-state HPA axis suppression (i.e., after desensitization has occurred), provide clinically useful benchmarks. For example, while oral prednisolone given at 20 mg QD produces a 73% cortisol suppression, even 5 mg QD (considered a "low dose") is associated with a 40% suppression of endogenous cortisol production. Doses at or below 5 mg of prednisolone per day are generally considered to be well tolerated and are not associated with clinically meaningful HPA axis suppression (La Rochelle et al., "Recovery of the hypothalamic-pituitary-adrenal (HPA) axis in patients with rheumatic diseases receiving low-dose prednisolone." *Am. J. Med.* 95 (1993): 258-264). Therefore, up to approximately 40% suppression will be clinically well

tolerated and very unlikely to be associated with importantly adverse clinical events such as hypoadrenalism or soft-tissue or bony or metabolic changes indicative of long-term glucocorticoid excess.

"Patient" refers to a human diagnosed with a disease or condition that can be treated in accordance to the inventions described herein. In some embodiments it is contemplated that the formulations described herein may also be used in horses.

"Delivery" refers to any means used to place the drug into a patient. Such means may include without limitation, placing matrices into a patient that release the drug into a target area. One of ordinary skill in the art recognizes that the matrices may be delivered by a wide variety of methods, e.g., injection by a syringe, placement into a drill site, catheter or canula assembly, or forceful injection by a gun type apparatus or by placement into a surgical site in a patient during surgery.

The terms "treatment" and "treating" a patient refer to reducing, alleviating, stopping, blocking, or preventing the symptoms of pain and/or inflammation in a patient. As used herein, "treatment" and "treating" includes partial alleviation of symptoms as well as complete alleviation of the symptoms for a time period. The time period can be hours, days, months, or even years.

By an "effective" amount or a "therapeutically effective amount" of a drug or pharmacologically active agent is meant a nontoxic but sufficient amount of the drug or agent to provide the desired effect, e.g., analgesia. An appropriate "effective" amount in any individual case may be determined by one of ordinary skill in the art using routine experimentation.

"Site of a patient's pain" refers to any area within a body causing pain, e.g., a knee joint with osteoarthritis, nerve root causing sciatic pain, nerve fibers growing into annular tears in discs causing back pain, temporomandibular joint (TMJ) pain, for example TMJ pain associated with temporomandibular joint disorder (TMD) or pain radiating from epidural or perineural spaces. The pain perceived by the patient may result from inflammatory responses, mechanical stimuli, chemical stimuli, thermal stimuli, as well as allodynia.

Additionally, the site of a patient's pain can comprise one or multiple sites in the spine, such as between the cervical, thoracic, or lumbar vertebrae, or can comprise one or multiple sites located within the immediate area of inflamed or injured joints such as the shoulder, hip, or other joints.

A "biocompatible" material refers to a material that is not toxic to the human body, it is not carcinogenic and it should induce limited or no inflammation in body tissues. A "biodegradable" material refers to a material that is degraded by bodily processes (e.g., enzymatic) to products readily disposable by the body or absorbed into body tissue. The biodegraded products should also be biocompatible with the body. In the context of intra-articular drug delivery systems for corticosteroids, such polymers may be used to fabricate, without limitation: microparticles, micro-spheres, matrices, microparticle matrices, micro-sphere matrices, capsules, hydrogels, rods, wafers, pills, liposomes, fibers, pellets, or other appropriate pharmaceutical delivery compositions that a physician can administer into the joint. The biodegradable polymers degrade into non-toxic residues that the body easily removes or break down or dissolve slowly and are cleared from the body intact. The polymers may be cured ex-vivo forming a solid matrix that incorporates the drug for controlled release to an inflammatory region. Suitable biodegradable polymers may include, without limitation natural or synthetic biocompatible biodegradable material. Natural polymers include, but are not limited to, proteins such as

albumin, collagen, gelatin synthetic poly(aminoacids), and prolamines; glycosaminoglycans, such as hyaluronic acid and heparin; polysaccharides, such as alginates, chitosan, starch, and dextrans; and other naturally occurring or chemically modified biodegradable polymers. Synthetic biocompatible biodegradable materials include, but are not limited to, poly(lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyhydroxybutyric acid, poly(trimethylene carbonate), polycaprolactone (PCL), polyvalerolactone, poly(alpha-hydroxy acids), poly(lactones), poly(amino-acids), poly(anhydrides), polyketals poly(arylates), poly(orthoesters), polyurethanes, polythioesters, poly(orthocarbonates), poly(phosphoesters), poly(ester-co-amide), poly(lactide-co-urethane, polyethylene glycol (PEG), polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer (polyactive), methacrylates, poly(N-isopropylacrylamide), PEO-PPO-PEO (pluronic), PEO-PPO-PAA copolymers, and PLGA-PEO-PLGA blends and copolymers thereof and any combinations thereof. The biocompatible biodegradable material can include a combination of biocompatible biodegradable materials. For example, the biocompatible biodegradable material can be a triblock, or other multi-block, formation where a combination of biocompatible biodegradable polymers are joined together. For example, the triblock can be PLGA-PEG-PLGA.

Diseases that May be Treated Using the Formulations of this Invention

Descriptions of various embodiments of the invention are given below. Although these embodiments are exemplified with reference to treat joint pain associated with osteoarthritis, rheumatoid arthritis and other joint disorders, it should not be inferred that the invention is only for these uses. Rather, it is contemplated that embodiments of the present invention will be useful for treating other forms of joint pain by administration into articular and periarticular spaces. In addition, it will be understood that for some embodiments injection near a joint may be equivalent to injections in that joint. It is also contemplated that embodiments of the present invention may be useful for injection or administration into soft tissues or lesions. Any and all uses of specific words and references are simply to detail different embodiments of the present invention.

Local administration of a corticosteroid microparticle formulation can occur, for example, by injection into the intra-articular space, peri-articular space, soft tissues, lesions, epidural space, perineural space, or the foraminal space at or near the site of a patient's pain and/or structural tissue damage. Local injection of the formulations described herein into articular or periarticular spaces may be useful in the treatment of, for example, juvenile rheumatoid arthritis, sciatica and other forms of radicular pain (e.g., arm, neck, lumbar, thorax), psoriatic arthritis, acute gouty arthritis, Morton's neuroma, acute and subacute bursitis, acute and subacute nonspecific tenosynovitis and epicondylitis, acute rheumatic carditis and ankylosing spondylitis. Injection of the microparticles described herein into soft tissues or lesions may be useful in the treatment of, for example, alopecia areata, discoid lupus, erythematosus, keloids, localized hypertrophic, infiltrated inflammatory lesions of granuloma annulare, lichen planus, lichen simplex chronicus (neurodermatitis), psoriasis and psoriatic plaques, necrobiosis lipoidica diabetorum, and psoriatic arthritis. Injection of the microparticles described herein into epidural spaces may be useful in the treatment of, for example, neurogenic claudication. Intramuscular or other soft tissues or lesions injections may also be useful in providing systemic exposures that are effective in the control of incapacitating allergic conditions (including but not limited

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to asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, seasonal or perennial allergic rhinitis, serum sickness, transfusion reactions), bullous dermatitis herpetiformis, exfoliative dermatitis, mycosis fungoides, pemphigus, severe erythema multiforme (Stevens-Johnson syndrome), Primary or secondary adrenocortical insufficiency in conjunction with mineralocorticoids where applicable; congenital adrenal hyperplasia, hypercalcemia associated with cancer, nonsupportive thyroiditis, exacerbations of regional enteritis and ulcerative colitis, acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond blackfan anemia), pure red cell aplasia, select cases of secondary thrombocytopenia, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used concurrently with appropriate antituberculous chemotherapy, palliative management of leukemias and lymphomas, acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor or craniotomy, to induce diuresis or remission of proteinuria in idiopathic nephrotic syndrome, or to induce diuresis or remission of proteinuria in lupus erythematosus, berylliosis, symptomatic sarcoidosis, fulminating or disseminated pulmonary tuberculosis (when used concurrently with appropriate antituberculous chemotherapy), idiopathic eosinophilic pneumonias, symptomatic sarcoidosis, dermatomyositis, polymyositis, and systemic lupus erythematosus, post-operative pain and swelling.

In one embodiment, the corticosteroid microparticle formulations provided herein are useful in treating, alleviating a symptom of, ameliorating and/or delaying the progression of sciatica. In one embodiment, corticosteroid microparticle formulations provided herein are useful in treating, alleviating a symptom of, ameliorating and/or delaying the progression of temporomandibular joint disorder (TMD).

In one embodiment, the corticosteroid microparticle formulations provided herein are useful in treating, alleviating a symptom of, ameliorating and/or delaying the progression of neurogenic claudication secondary to lumbar spinal stenosis (LSS). LSS implies spinal canal narrowing with possible subsequent neural compression (classified by anatomy or etiology). Neurogenic Claudication (NC) is a hallmark symptom of lumbar stenosis, in which the column of the spinal cord (or the canals that protect the nerve roots) narrows at the lower back. This narrowing can also occur in the spaces between the vertebrae where the nerves leave the spine to travel to other parts of the body.

The microparticles of the invention are used to treat, alleviate a symptom of, ameliorate and/or delay the progression patients suffering from NC secondary to LSS. The corticosteroid microparticle formulations can be administered, for example, by epidural steroid injection (ESI).

Administration of a corticosteroid microparticle formulation, e.g., a TCA microparticle formulation, to a patient suffering from an inflammatory disease such as osteoarthritis or rheumatoid arthritis, is considered successful if any of a variety of laboratory or clinical results is achieved. For example, administration of a corticosteroid microparticle formulation is considered successful if one or more of the symptoms associated with the disease is alleviated, reduced, inhibited or does not progress to a further, i.e., worse, state. Administration of a corticosteroid microparticle formulation is considered successful if the disease, e.g., an arthritic or other inflammatory disease, enters remission or does not progress to a further, i.e., worse, state.

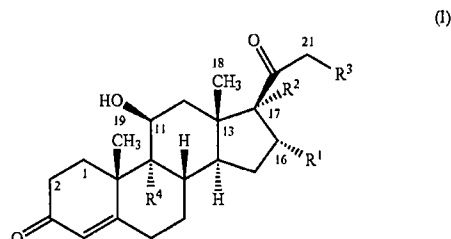
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Also, any and all alterations and further modifications of the invention, as would occur to one of ordinary skill in the art, are intended to be within the scope of the invention

Selection of Corticosteroids and Drug Dosage

Corticosteroids associated with embodiments of the present invention can be any naturally occurring or synthetic steroid hormone. Naturally occurring corticosteroids are secreted by the adrenal cortex or generally the human body.

Corticosteroid molecules have the following basic structure:



Corticosteroids have been classified into four different groups (A, B, C, and D). (See e.g., Foti et al. "Contact Allergy to Topical Corticosteroids: Update and Review on Cross-Sensitization." *Recent Patents on Inflammation & Allergy Drug Discovery* 3 (2009): 33-39; Coopman et al., "Identification of cross-reaction patterns in allergic contact dermatitis to topical corticosteroids." *Br J Dermatol* 121 (1989): 27-34). Class A corticosteroids are hydrocortisone types with no modification of the D ring or C20-C21 or short chain esters on C20-C21. Main examples of Class A corticosteroids include prednisolone, hydrocortisone and methylprednisolone and their ester acetate, sodium phosphate and succinate, cortisone, prednisone, and tixocortol pivalate. Class B corticosteroids are triamcinolone acetonide (TCA) types with cis/ketalic or diolic modifications on C16-C17. Main examples of Class B corticosteroids include triamcinolone acetonide (TCA), flucinolone acetonide, amcinonide, desonide, fluocinonide, halcinonide, budesonide, and flunisolide. Class C corticosteroids are betamethasone types with a —CH₃ mutation on C16, but no esterification on C17-C21. Main examples of Class C corticosteroids include betamethasone, dexamethasone, desoxymethasone, flucortolone, and halomethasone. Class D corticosteroids are clobetasone or hydrocortisone esterified types with a long chain on C17 and/or C21 and with no methyl group on C16. Main examples of Class D corticosteroids include fluticasone, clobetasone butyrate, clobetasol propionate, hydrocortisone-17-aceponate, hydrocortisone-17-butyrate, beclomethasone dipropionate, betamethasone-17-valerate, betamethasone dipropionate, methylprednisolone aceponate, and prednicarbate.

For the present invention non-limiting examples of corticosteroids may include: betamethasone, betamethasone acetate, betamethasone dipropionate, betamethasone 17-valerate, cortivazol, dexamethasone, dexamethasone acetate, dexamethasone sodium phosphate, hydrocortisone, hydrocortisone aceponate, hydrocortisone acetate, hydrocortisone butyrate, hydrocortisone cypionate, hydrocortisone probutate, hydrocortisone sodium phosphate, hydrocortisone sodium succinate, hydrocortisone valerate, methylprednisolone, methylprednisolone aceponate, methylprednisolone acetate, methylprednisolone sodium succinate, prednisolone, prednisolone acetate, prednisolone metasulphobenzoate, prednisolone sodium phosphate, prednisolone steaglate,

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prednisolone tebutate, triamcinolone, triamcinolone acetonide, triamcinolone acetonide 21-palmitate, triamcinolone benetonide, triamcinolone diacetate, triamcinolone hexacetonide, alclometasone, alclometasone dipropionate, amcinonide, amelometasone, beclomethasone, beclomethasone dipropionate, beclomethasone dipropionate monohydrate, budesonide, butixocort, butixocort propionate, ciclesonide, ciprocinonide, clobetasol, clobetasol propionate, clocortolone, clobetasone, clobetasone butyrate, clocortolone pivalate, cloprednol, cortisone, cortisone acetate, deflazacort, domoprednate, deprodone, deprodone propionate, desonide, desoximetasone, desoxycortone, desoxycortone acetate, dichlorisone, diflorasone, diflorasone diacetate, difluocortolone, difluprednate, flucorolone, flucorolone acetonide, fludrocortisone, fludrocortisone acetate, fludroxycortide, flumethasone, flumethasone pivalate, flunisolide, fluocinolone, fluocinolone acetonide, fluocortin, fluocortolone, fluorometholone, fluticasone, fluticasone furoate, fluticasone propionate, fluorometholone acetate, fluoxymesterone, fluperolone, fluprednidene, fluprednidene acetate, fluprednisolone, formocortol, halcinonide, halobetasol propionate, halometasone, halopredone, halopredone acetate, hydrocortamate, isoflupredone, isoflupredone acetate, itrocinnonide, loteprednol etabonate, mazipredone, meclorisone, meclorisone dibutyrate, medrysone, meprednisone, mometasone, mometasone furoate, mometasone furoate monohydrate, nivacortol, paramethasone, paramethasone acetate, prednazoline, prednicarbate, prednisolone, prednylidene, procinnonide, rofleponide, rimexolone, timobesone, tipredane, tixocortol, tixocortol pivalate and tralonide.

Embodiments of the invention include using sustained release corticosteroids delivered to treat pain at dosages that do not adversely suppress the HPA axis. Such amounts delivered locally to relieve pain due to inflammation, will provide a systemic concentration that does not have a measurable adverse effect on the HPA axis (differences if any are not significant because any such differences are within normal assay variability) or, as desired, may have a measurable but clinically insignificant effect on the HPA axis (basal cortisol is suppressed to some measurable extent but stress responses are adequately preserved). Further embodiments of the invention include doses during a second period of time selected to adjust for a change in sensitivity of the HPA axis to suppression following exposure during a first period of time to the corticosteroid (FIG. 1).

Additional embodiments include doses during first and/or the second period of time selected to adjust for corticosteroid-specific (or corticosteroid- and potentially dose-specific) changes in the rate of change of sensitivity of the HPA axis to suppression that begin with initial exposure. For clinically effective corticosteroids, the rate of change of the sensitivity of the HPA axis to exogenous corticosteroids is both non-uniform and non-linear (FIG. 2). The rate and pattern of change in such sensitivity varies widely as a function of the particular corticosteroid that is selected (FIG. 3).

Finally, it is possible to usefully characterize the change in sensitivity vs. time mathematically as the (non-linear, exponential) "decay" of the sensitivity from the initial to final value, wherein the decay parameters (Table 1) has been determined from the data further described herein.

TABLE 1

HPA Axis Change-in-Sensitivity Decay-Parameter δ vs. Corticosteroid and Dose *	
Corticosteroid	Decay Parameter δ (time ⁻¹)
Betamethasone Phosphate/Acetate (7 mg)	0.024
Triamcinolone Acetonide (40 mg)	0.005
Triamcinolone Hexacetonide (20 mg)	0.070

* The inhibition of endogenous cortisol synthesis can be related to the exogenous corticosteroid concentration by the following equations:
 $E = (E_{max} \cdot C^n) / (EC_{50}^n + C^n)$ wherein E = effect, E_{max} = maximal effect, C = concentration of exogenous corticosteroid, EC_{50} = concentration at $1/2 E_{max}$, and n = the Hill ("slope"), or "slope" factor; and
 $EC_{50-final} = EC_{50-initial} + [EC_{50-final} - EC_{50-initial}] \cdot [1 - e^{(-\delta \cdot time)}]$

Using this approach permits the determination of "δ", the parameter describing the exponential decay from the initial to the final EC_{50} . Minimization of least-squares differences was utilized to obtain the best-fit δ.

These new findings regarding the rate and pattern of change of sensitivity to inhibition and the lack of predictability of such rates and patterns on the basis of, for example, steroid potency, have significant implications for clinically appropriate dose-selection. Those skilled in the art will appreciate the importance of a changing sensitivity to HPA axis suppression and will also appreciate both the complexity and counterintuitive aspects of several of these new findings (Table 1).

As a result of these clinical findings, the dose range to achieve clinically useful analgesia, with minimal or controlled modulation of the HPA axis, at steady state concentrations of various corticosteroids has been determined (Table 2). In particular, it appears that the daily corticosteroid doses at steady state concentrations, are approximately 3- to 7-times greater than are predicted by prior art (Meibohm, 1999).

TABLE 2

Dose (mg/d), adjusted for individual intra-articular corticosteroid characteristics, for expected suppression of endogenous cortisol production at steady state.					
Corticosteroid	Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
betamethasone (mg/d)	0.1	0.2	0.5	1.0	1.8
budesonide (mg/d)	0.1	0.2	0.6	1.2	2.2
des-ciclesonide (mg/d)	3.0	6.3	14.3	30.7	57.0
dexamethasone (mg/d)	0.1	0.2	0.4	0.9	1.6
flunisolide (mg/d)	0.3	0.5	1.2	2.6	4.8
fluticasone (mg/d)	0.1	0.1	0.3	0.6	1.1
mometasone (mg/d)	0.2	0.4	0.9	2.0	3.7
methylprednisolone (mg/d)	0.3	0.7	1.6	3.5	6.5
prednisolone (mg/d)	0.4	0.8	1.9	4.0	7.5
triamcinolone acetonide (mg/d)	0.2	0.4	0.8	1.7	3.2
triamcinolone hexacetonide (mg/d)	0.1	0.2	0.4	0.9	1.6

TABLE 2A

Total Dose Delivered (mg/month), adjusted for individual intra-articular corticosteroid characteristics, for expected suppression of endogenous cortisol production at steady state.					
Corticosteroid	Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
betamethasone	3.0	6.0	15.0	30.0	54.0
budesonide	3.0	6.0	18.0	36.0	66.0

TABLE 2A-continued

Total Dose Delivered (mg/month), adjusted for individual intra-articular corticosteroid characteristics, for expected suppression of endogenous cortisol production at steady state.					
Corticosteroid	Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
des-ciclesonide	90.0	189.0	429.0	921.0	1710.0
dexamethasone	3.0	6.0	12.0	27.0	48.0
flunisonide	9.0	15.0	36.0	78.0	144.0
fluticasone	3.0	3.0	9.0	18.0	33.0
mometasone	6.0	12.0	27.0	60.0	111.0
methylprednisolone	9.0	21.0	48.0	105.0	195.0
prednisolone	12.0	24.0	57.0	120.0	225.0
triamcinolone acetonide	6.0	12.0	24.0	51.0	96.0
triamcinolone hexacetonide	3.0	6.0	12.0	27.0	48.0

That higher doses of corticosteroids can be administered successfully by intra-articular injection, maximizing the likelihood of observing anti-inflammatory and analgesic responses while minimizing or eliminating adverse events from HPA axis suppression or otherwise excessive tissue exposure, is of profound clinical consequence for improving the treatment of patients with arthritis.

In addition, with these continuous daily doses of intra-articular corticosteroids, it is possible to determine the related systemic plasma level concentrations (Table 3) that will produce the target cortisol inhibition and not beyond, this while retaining clinically important anti-inflammatory and analgesic activity within the joint. These plasma concentrations were predicted on the basis of data from short term (i.e., less than 8 days) exposure to corticosteroids. With longer exposure to corticosteroids, the “decay” (i.e., decline) of the sensitivity to corticosteroids may continue resulting in values higher than those listed in Table 3. The levels calculated in Table 3 were purely hypothetical calculations based on human data with immediate release-level doses from the literature. With sustained release dosages, more drug may be able to be delivered without seeing an increased level of cortisol inhibition after the initial burst period. A given level of plasma concentration may actually provide less inhibition that would have been predicted or calculated using the human IR levels from the literature.

TABLE 3

Plasma corticosteroid concentrations associated with target levels of cortisol inhibition at steady state.					
Corticosteroid	Corticosteroid Concentration in Plasma (ng/mL) associated with the Target Levels of Cortisol Inhibition (%)				
	5%	10%	20%	35%	50%
betamethasone (ng/mL)	0.33	0.70	1.57	3.38	6.27
budesonide (ng/mL)	0.60	1.27	2.85	6.14	11.40
des-ciclesonide (ng/mL)	0.55	1.16	2.61	5.63	10.45
dexamethasone (ng/mL)	0.21	0.44	1.00	2.15	3.99
flunisonide (ng/mL)	0.18	0.38	0.86	1.84	3.42
fluticasone (ng/mL)	0.04	0.08	0.19	0.41	0.76
mometasone (ng/mL)	0.15	0.32	0.71	1.54	2.85
methylprednisolone (ng/mL)	0.68	1.44	3.23	6.96	12.92
prednisolone (ng/mL)	1.64	3.46	7.79	16.79	31.16
triamcinolone acetonide (ng/mL)	0.19	0.40	0.90	1.95	3.61
triamcinolone hexacetonide (ng/mL)	0.10	0.21	0.48	1.02	1.90

The studies presented herein demonstrate for the first time the discovery of the time-course of changes in sensitivity of

the HPA axis to exogenous corticosteroids. In addition, both the mean doses and mean plasma levels shown in Tables 2 and 3 above are those after steady state has been achieved, requiring approximately 4 to 24 days depending upon the corticosteroid in question. The companion post-dose but pre-steady-state transients for several corticosteroids have been described in FIGS. 2, 3, and 4. It is also important to note that the data suggest that the carefully controlled benefits from the intra-articular, sustained release of a corticosteroid of interest will persist as long as release continues.

In one preferred embodiment, a single component sustained release formulation releases a dose (in mg/day) that suppresses the HPA axis by no more than between 5-40% at steady state as shown in Table 2, more preferably no more than between 10-35% at steady state as shown in Table 2. These doses are therapeutically effective without adverse side effects.

In another preferred embodiment, a single component sustained release formulation releases a dose (in mg/day) that does not measurably suppress the HPA axis at steady state. These doses are therapeutically effective without adverse side effects.

In another embodiment where both an immediate release component and sustained release component of the formulation are present, immediate release dose would be as shown in Table 4 and the sustained release dose would be a dose (in mg/day) that suppresses the HPA axis by no more than between 5-40% as shown in Table 2, more preferably no more than between 10-35% as shown in Table 2. In addition, it is expected that sustained release doses described previously will follow immediate release doses as shown in Table 4.

TABLE 4

Immediate release relative doses (mg)	
Corticosteroid	Immediate Release Dose (mg)
betamethasone ¹	5-20
budesonide ²	7-28
des-ciclesonide ²	177-713
dexamethasone ²	5-20
flunisonide ²	15-60
fluticasone ²	3-12
mometasone ²	11-44
methylprednisolone ¹	40-160
prednisolone ¹	25-100
triamcinolone acetonide ¹	10-40
triamcinolone hexacetonide ¹	10-40

¹clinical doses
²calculated doses

Sustained Release Delivery Platforms

The manufacture of microparticles or methods of making biodegradable polymer microparticles are known in the art. Microparticles from any of the biodegradable polymers listed below can be made by, but not limited to, spray drying, solvent evaporation, phase separation, spray drying, fluidized bed coating or combinations thereof.

In certain embodiments of the invention, the microparticles are made from a biodegradable polymer that may include, without limitation, natural or synthetic biocompatible biodegradable materials. Natural polymers include, but are not limited to, proteins such as albumin, collagen, gelatin synthetic poly(aminoacids), and prolamines; glycosaminoglycans, such as hyaluronic acid and heparin; polysaccharides, such as alginates, chitosan, starch, and dextrans; and other naturally occurring or chemically modified biodegradable polymers. Synthetic biocompatible biodegradable materials

include, but are not limited to the group comprising of, poly (lactide-co-glycolide) (PLGA), polylactide (PLA), polyglycolide (PG), polyhydroxybutyric acid, poly(trimethylene carbonate), polycaprolactone (PCL), polyvalerolactone, poly (alpha-hydroxy acids), poly(lactones), poly(amino-acids), poly(anhydrides), polyketals poly(arylates), poly(orthoesters), poly(orthocarbonates), poly(phosphoesters), poly(ester-co-amide), poly(lactide-co-urethane), polyethylene glycol (PEG), polyvinyl alcohol (PVA), PVA-g-PLGA, PEGT-PBT copolymer(polyactive), polyurethanes, polythioesters, methacrylates, poly(N-isopropylacrylamide), PEO-PPO-PEO (pluronic), PEO-PPO-PAA copolymers, and PLGA-PEO-PLGA blends and copolymers thereof, multi-block polymer configurations such as PLGA-PEG-PLGA, and any combinations thereof. These polymers may be used in making controlled release or sustained release compositions disclosed herein.

In a preferred embodiment, the microparticles are formed from poly(D,L-lactic-co-glycolic acid) (PLGA), which is commercially available from a number of sources. Biodegradable PLGA copolymers are available in a wide range of molecular weights and ratios of lactic to glycolic acid. If not purchased from a supplier, then the biodegradable PLGA copolymers may be prepared by the procedure set forth in U.S. Pat. No. 4,293,539 (Ludwig, et al.), the disclosure of which is hereby incorporated by reference in its entirety. Ludwig prepares such copolymers by condensation of lactic acid and glycolic acid in the presence of a readily removable polymerization catalyst (e.g., a strong acid ion-exchange resin such as Dowex HCR-W2-H). However, any suitable method known in the art of making the polymer can be used.

In the coacervation process, a suitable biodegradable polymer is dissolved in an organic solvent. Suitable organic solvents for the polymeric materials include, but are not limited to acetone, halogenated hydrocarbons such as chloroform and methylene chloride, aromatic hydrocarbons such as toluene, halogenated aromatic hydrocarbons such as chlorobenzene, and cyclic ethers such as dioxane. The organic solvent containing a suitable biodegradable polymer is then mixed with a non-solvent such as silicone based solvent. By mixing the miscible non-solvent in the organic solvent, the polymer precipitates out of solution in the form of liquid droplets. The liquid droplets are then mixed with another non-solvent, such as heptane or petroleum ether, to form the hardened microparticles. The microparticles are then collected and dried. Process parameters such as solvent and non-solvent selections, polymer/solvent ratio, temperatures, stirring speed and drying cycles are adjusted to achieve the desired particle size, surface smoothness, and narrow particle size distribution.

In the phase separation or phase inversion procedures entrap dispersed agents in the polymer to prepare microparticles. Phase separation is similar to coacervation of a biodegradable polymer. By addition of a nonsolvent such as petroleum ether, to the organic solvent containing a suitable biodegradable polymer, the polymer is precipitates from the organic solvent to form microparticles.

In the salting out process, a suitable biodegradable polymer is dissolved in an aqueous miscible organic solvent. Suitable water miscible organic solvents for the polymeric materials include, but are not limited to acetone, as acetone, acetonitrile, and tetrahydrofuran. The water miscible organic solvent containing a suitable biodegradable polymer is then mixed with an aqueous solution containing salt. Suitable salts include, but are not limited to electrolytes such as magnesium chloride, calcium chloride, or magnesium acetate and non-electrolytes such as sucrose. The polymer precipitates from the organic solvent to form microparticles, which are col-

lected and dried. Process parameters such as solvent and salt selection, polymer/solvent ratio, temperatures, stirring speed and drying cycles are adjusted to achieve the desired particle size, surface smoothness, and narrow particle size distribution.

Alternatively, the microparticles may be prepared by the process of Ramstack et al., 1995, described in published international patent application WO 95/13799, the disclosure of which is incorporated herein in its entirety. The Ramstack et al. process essentially provides for a first phase, including an active agent and a polymer, and a second phase, that are pumped through a static mixer into a quench liquid to form microparticles containing the active agent. The first and second phases can optionally be substantially immiscible and the second phase is preferably free from solvents for the polymer and the active agent and includes an aqueous solution of an emulsifier.

In the spray drying process, a suitable biodegradable polymer is dissolved in an organic solvent and then sprayed through nozzles into a drying environment provided with sufficient elevated temperature and/or flowing air to effectively extract the solvent. Adding surfactants, such as sodium lauryl sulfate can improve the surface smoothness of the microparticles.

Alternatively, a suitable biodegradable polymer can be dissolved or dispersed in supercritical fluid, such as carbon dioxide. The polymer is either dissolved in a suitable organic solvent, such as methylene chloride, prior to mixing in a suitable supercritical fluid or directly mixed in the supercritical fluid and then sprayed through a nozzle. Process parameters such as spray rate, nozzle diameter, polymer/solvent ratio, and temperatures, are adjusted to achieve the desired particle size, surface smoothness, and narrow particle size distribution.

In a fluidized bed coating, the drug is dissolved in an organic solvent along with the polymer. The solution is then processed, e.g., through a Wurster air suspension coating apparatus to form the final microcapsule product.

The microparticles can be prepared in a size distribution range suitable for local infiltration or injection. The diameter and shape of the microparticles can be manipulated to modify the release characteristics. In addition, other particle shapes, such as, for example, cylindrical shapes, can also modify release rates of a sustained release corticosteroid by virtue of the increased ratio of surface area to mass inherent to such alternative geometrical shapes, relative to a spherical shape. The microparticles have a mass mean diameter ranging between about 0.5 to 500 microns. In a preferred embodiment, the microparticles have a mass mean diameter of between 10 to about 100 microns.

Biodegradable polymer microparticles that deliver sustained release corticosteroids may be suspended in suitable aqueous or non-aqueous carriers which may include, but is not limited to water, saline, pharmaceutically acceptable oils, low melting waxes, fats, lipids, liposomes and any other pharmaceutically acceptable substance that is lipophilic, substantially insoluble in water, and is biodegradable and/or eliminatable by natural processes of a patient's body. Oils of plants such as vegetables and seeds are included. Examples include oils made from corn, sesame, cannoli, soybean, castor, peanut, olive, arachis, maize, almond, flax, safflower, sunflower, rape, coconut, palm, babassu, and cottonseed oil; waxes such as carnoba wax, beeswax, and tallow; fats such as triglycerides, lipids such as fatty acids and esters, and liposomes such as red cell ghosts and phospholipid layers.

Corticosteroid Loading of and Release from Biodegradable Polymer Microparticles

When an intra-articularly delivered corticosteroid is incorporated into a biodegradable polymer for sustained release into a joint at a dosage that does not suppress the HPA axis, preferred loadings of said corticosteroid are from about 5% to about 40% (w/w) of the polymer, preferably about 5% to about 30%, more preferably about 5% to about 28% of the polymer.

As the biodegradable polymers undergo gradual bio-erosion within the joint, the corticosteroid is released to the inflammatory site. The pharmacokinetic release profile of the corticosteroid by the biodegradable polymer may be first order, zero order, bi- or multi-phasic, to provide desired treatment of inflammatory related pain. In any pharmacokinetic event, the bio-erosion of the polymer and subsequent release of the corticosteroid may result in a controlled release of a corticosteroid from the polymer matrix. The rate of release at dosages that do not suppress the HPA axis are described above.

Excipients

The release rate of the corticosteroid from a biodegradable polymer matrix can be modulated or stabilized by adding a pharmaceutically acceptable excipient to the formulation. An excipient may include any useful ingredient added to the biodegradable polymer depot that is not a corticosteroid or a biodegradable polymer. Pharmaceutically acceptable excipients may include without limitation lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, PEG, polysorbate 20, polysorbate 80, polyvinylpyrrolidone, cellulose, water, saline, syrup, methyl cellulose, and carboxymethyl cellulose. An excipient for modulating the release rate of a corticosteroid from the biodegradable drug depot may also include without limitation pore formers, pH modifiers, reducing agents, antioxidants, and free radical scavengers.

Delivery of Corticosteroid Microparticles

Parenteral administration of formulations of the invention can be effected by intra-articular injection or other injection using a needle. To inject the microparticles into a joint, needles having a gauge of about 14-28 gauge are suitable. It will be appreciated by those skilled in the art that formulations of the present invention may be delivered to a treatment site by other conventional methods, including catheters, infusion pumps, pens devices, injection guns and the like.

All references, patents, patent applications or other documents cited are hereby incorporated by reference.

EXAMPLES

The present invention is further defined in the following Examples. It should be understood that these Examples, while indicating preferred embodiments of the invention, are given by way of illustration only. From the above discussion and these Examples, one skilled in the art can ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various uses and conditions.

Example 1**Sustained-Release Betamethasone or Triamcinolone Acetonide Microparticles**

In one embodiment, the microparticle formulation contains a copolymer of DL-lactide (or L-lactide) and glycolide

in a 45:55 molar ratio (up to 75:25 molar ratio) with an inherent viscosity ranging from 0.15 to 0.60 dL/g with either an ester or acid end group plus either the corticosteroid betamethasone or triamcinolone acetonide. If betamethasone is used, then the betamethasone is in the form of either betamethasone acetate, betamethasone dipropionate or a combination thereof. The total amount of betamethasone or triamcinolone acetonide incorporated into the microparticle ranges from 10% to 30% (w/w). The microparticles are formulated to mean mass range in size from 10 to 100 microns. The population of microparticles is formulated to be delivered through a 19 gauge or higher needle. Additional excipients may be added such as, but not limited to, carboxymethylcellulose sodium, mannitol, polysorbate-80, sodium phosphate, sodium chloride, polyethylene glycol to achieve isotonicity and promote syringeability. If betamethasone is used, then the betamethasone incorporated into the microparticle population provides an initial release (burst) of about 5-20 mg of drug over a period of 1 to 12 hours, followed by a steady state release of drug at a rate of about 0.1 to 1.0 mg/day over a period of 14 to 90 days. If triamcinolone acetonide is used, then the drug incorporated into the microparticle population provides an initial release (burst) of about 10-40 mg of drug over a period of 1 to 12 hours, followed by a steady state release of drug at a rate of about 0.2 to 1.7 mg/day over a period of 14 to 90 days.

Example 2**Sustained-Release Betamethasone or Triamcinolone Acetonide Microparticles with an Immediate Release Form**

In another embodiment, the microparticle formulation of Example 1 is further admixed with an immediate release betamethasone or triamcinolone acetonide component, such as a betamethasone or triamcinolone acetonide containing solution. If betamethasone is used, then the betamethasone in the immediate release component is in the form of either betamethasone acetate, betamethasone dipropionate or a combination thereof. If betamethasone is used, then the immediate release component provides an initial release of a total of about 5 to 20 mg of betamethasone over the first 1-10 days, while the sustained release component releases betamethasone at a rate of about 0.1 to 1.0 mg/day over the first 14 to 90 days following administration. If triamcinolone acetonide is used, then the immediate release component provides an initial release of a total of 10 to 40 mg of drug over the first 1-10 days, while the sustained release component releases drug at a rate of about 0.2 to 1.7 mg/day over the first 14 to 90 days following administration.

Example 3**Determination of Time-Variance in HPA Axis Sensitivity**

Adult volunteers (N=4 to 9 per group) give appropriate informed consent. Each individual in each group receives a single intra-articular administration of an exogenous corticosteroid (triamcinolone acetonide 40 mg; triamcinolone hexacetonide 20; betamethasone 7 mg (disodium phosphate 4 mg/acetate 3 mg). Blood samples for measurement of corticosteroid concentrations and/or cortisol concentrations are drawn at 8 AM at baseline and on days 1, 7, 9, 10, 12, 14, 18, and 21. The extent of suppression of endogenous cortisol was measured in each subject in each group. The extent of cortisol

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suppression predicted by previously published models (Meibohm, 1999) was determined and compared to observations (FIG. 4 Column 1). The change (decrease) in HPA axis sensitivity vs. time is then determined on a day-by-day and final basis (FIG. 4, Column 2), permitting determination of the correct steady-state intra-articular doses of corticosteroid to achieve, or limit, HPA axis suppression to the desired level.

Example 4

Preparation of Triamcinolone Acetonide Microparticles by Spinning Disk

A pharmaceutical depot was prepared comprised of the corticosteroid, triamcinolone acetonide (TCA, 9 α -Fluoro-11 β ,16 α ,17 α ,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-acetonide; 9 α -Fluoro-16 α -hydroxyprednisolone 16 α ,17 α -acetonide) incorporated into PLGA microparticles.

In one suitable thirty day formulation, 250 mg of triamcinolone acetonide and 750 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.4 dL/g and molecular weight of 54 kDa) were dispersed in 14.25 grams of dichloromethane. The dispersion was atomized into microdroplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 μ m sieve.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Malvern Mastersizer 2000) by dispersing a 250 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. Sonication was maintained as the sample was stirred at 2500 rpm and measurements taken every 15 seconds, with the average of three measurements reported. 10 mg of TCA containing microparticles were added to 10 mL of dimethylsulfoxide (DMSO), mixed until dissolved and an aliquot analyzed by HPLC to determine the microparticle drug load. Another 4 mg of TCA containing microparticles were suspended in 20 mL of phosphate buffered saline (PBS) containing 0.5% sodium dodecyl sulfate (SDS) maintained at 37° C. 0.5 mL of the media was removed at regular intervals, replaced at each interval with an equivalent amount of fresh media to maintain a constant volume, and analyzed by HPLC to determine microparticle in vitro release. Analysis by HPLC was conducted using a C18 (Waters Nova-Pack C-18, 3.9 $\times$ 150 mm) and 35% acetonitrile mobile phase at 1 mL/min flow rate with UV detection at 240 nm. The results are shown in Table 5.

TABLE 5

Analytical Results for 25% Triamcinolone Acetonide PLGA 75:25 Microparticles				
PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)
75:25	24	96	D0.1: 32 μ m	0.2 day: 5.1
carboxylic acid end-capped			D0.5: 49 μ m	1 day: 13.5
0.4 dL/g			D0.9: 73 μ m	3 day: 29.6
				7 day: 52.6

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TABLE 5-continued

Analytical Results for 25% Triamcinolone Acetonide PLGA 75:25 Microparticles				
PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)
54 kDa				14 day 70.9
25%				21 day: 76.4
				28 day: 79.1

The in vitro cumulative release profile is graphed in FIG. 5.

In one iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would achieve a transient suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% as shown in FIG. 6. In a second iteration of these data, the amount of triamcinolone acetonide released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35% as shown in FIG. 7. These calculated doses equal 376 mg of microparticles containing 94 mg of TCA and 80 mg of microparticles containing 20 mg of TCA, respectively.

In a second preparation of the same formulation, analyzed and in vitro release plotted in the same manner, the results are equivalent as shown in Table 6, and FIGS. 8, 9 and 10. The calculated human dose, as exemplified in Table 2 that would achieve a transient suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% equals 280 mg of microparticles containing 70 mg of TCA. The calculated human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35% equals 68 mg of microparticles containing 17 mg of TCA.

TABLE 6

Analytical Results for Alternate Preparation of a Nominal 25% Triamcinolone Acetonide PLGA 75:25 Microparticles				
PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)
75:25	27.5	110	D0.1: 30.9 μ m	0.2 day: 4.8
carboxylic acid end-capped			D0.5: 48.2 μ m	1 day: 15
0.4 dL/g			D0.9: 71.0 μ m	3 day: 28.5
54 kDa				7 day: 50.2
25%				14 day 67.1
				21 day: 74.2
				28 day: 75.7

Influence of PEG on PLGA 75:25 Formulations

In other suitable formulations, polyethylene glycol was added to the PLGA 75:25 polymers while keeping the target amount of triamcinolone acetonide constant. PEG/PLGA blends are known to allow for more complete and faster release of pharmaceutical agents incorporated into microparticles than PLGA alone (Cleck et al. "Microparticles of poly

(DL-lactic-coglycolic acid)/poly(ethylene glycol) blends for controlled drug delivery." *J Control Release* 48 (1997): 259-268; Morlock, et al. "Erythropoietin loaded microspheres prepared from biodegradable LPLG-PEO-LPLG triblock copolymers: protein stabilization and in-vitro release properties." *J Control Release*, 56 (1-3) (1998): 105-15; Yeh, "The stability of insulin in biodegradable microparticles based on blends of lactide polymers and polyethylene glycol." *J Microencapsul*, 17(6) (2000): 743-56).

In one iteration, 250 mg of triamcinolone acetonide, 50 mg of polyethylene glycol (PEG 1450) and 700 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.4 dL/g and molecular weight of 54 kDa) were dispersed in 14 grams of dichloromethane. In another iteration, 250 mg of triamcinolone acetonide, 100 mg of polyethylene glycol (PEG 3350) and 650 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.4 dL/g and molecular weight of 54 kDa) were dispersed in 13 grams of dichloromethane. The dispersions were atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 µm sieve.

The microparticles were analyzed as described above and the data is shown in Table 7.

TABLE 7

Analytical Results of Nominal 25% Triamcinolone Acetonide PLGA 75:25 Microparticles containing Polyethylene Glycol (PEG) Additive				
PLGA(lactide:glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, µm)	In vitro release (%)
75:25 carboxylic acid end-capped 0.4 dL/g 54 kDa 25% 5% PEG 1450	29.4	118	D0.1: 36.2 µm D0.5: 59.0 µm D0.9: 95.5 µm	0.2 day: 3.6 1 day: 13.8 3 day: 30.1 7 day: 49.5 14 day 65.5 21 day: 74.0 28 day: 78.5
75:25 carboxylic acid end-capped 0.4 dL/g 54 kDa 25% 10% PEG 3350	24.5	98	D0.1: 32.0 µm D0.5: 52.4 µm D0.9: 79.0 µm	0.2 day: 4.1 1 day: 11.7 3 day: 24.5 7 day: 40.8 14 day: 55.8 21 day: 63.7 28 day: 69.5

The in vitro cumulative release profile is graphed in FIG. 11 and FIG. 12. PEG did not seem to enhance the release of the TCA in either formulation, as would be expected. In fact, at higher percentages of PEG, albeit a different molecular weight (higher percentages of PEG 1350 were unmanageable due to the agglomeration of microparticles), the release rate was slower.

In one iteration of these in vitro release data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% as shown in FIG. 13 and FIG. 14. These calculated doses equal 296 mg of microparticles containing 74 mg of TCA and 316 mg of microparticles contain-

ing 79 mg of TCA, respectively. In a second iteration of these data, the amount of triamcinolone acetonide released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35% as shown in FIGS. 15 and 16. These calculated doses equal 68 mg of microparticles containing 17 mg of TCA and 88 mg of microparticles containing 22 mg of TCA, respectively.

Other TCA containing formulations were tried with PEG and PLGA 75:25 without success. A PLGA microparticle formulation containing 25% TCA and 25% PEG 1450 agglomerated during manufacture and storage. Another PLGA formulation containing 40% TCA and 15% PEG 1450 gave similar results to the microparticles containing 40% TCA and no PEG.

Influence of Triamcinolone Acetonide Content in PLGA 75:25 Microparticles:

Triamcinolone acetonide containing microparticle depots were prepared and analyzed, as described above, with the exception of using 100 mg, 150 mg, 200 mg and 400 mg triamcinolone acetonide and adding to a 5% PLGA dichloromethane solution. The physical characteristics of these formulations are shown in Table 8.

TABLE 8

Analytical Results of PLGA 75:25 Microparticles containing varying amounts of Triamcinolone Acetonide					
PLGA(lactide:glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA	Drug load (% TCA by weight)	Incorporation efficiency (%)	Particle size (Dv, µm)	In vitro release (%)	
75:25 carboxylic acid end-capped 0.4 dL/g 54 kDa 40%	43.4	109	D0.1: 40.7 µm D0.5: 70.7 µm D0.9: 167 µm	0.2 day: 6.6 1 day: 24.2 3 day: 53.8 7 day: 82.5 14 day 89.4 21 day: 89.6 28 day: 87.5	
75:25 carboxylic acid end-capped 0.4 dL/g 54 kDa 20%	20.2	101	D0.1: 28.7 µm D0.5: 45.2 µm D0.9: 70.5 µm	0.2 day: 5.3 1 day: 13.5 3 day: 23.7 7 day: 35.3 14 day 44.4 21 day: 48.1 28 day: 50.6	
75:25 carboxylic acid end-capped 0.4 dL/g 54 kDa 15%	15.9	106	D0.1: 30.7 µm D0.5: 47.8 µm D0.9: 74.8 µm	0.2 day: 3.9 1 day: 9.0 3 day: 14.2 7 day: 19.3 14 day 22.7 21 day: 24.6 28 day: 27.6	
75:25 carboxylic acid end-capped 0.4 dL/g 54 kDa 10%	11.7	117	D0.1: 31.0 µm D0.5: 57.9 µm D0.9: 118 µm	0.2 day: 2.3 1 day: 4.4 3 day: 5.9 7 day: 7.5 14 day 9.9 21 day: 11.7 28 day: 15.8	

The in vitro cumulative release profiles for these four other TCA containing PLGA 75:25 microparticle depots are graphed in FIG. 17, along with the preferred formulation (25% TCA). The tabulated data and graph show the impact of the percent TCA incorporated in the PLGA microparticles on the in vitro release profile. The 10%, 15% and 20% TCA containing PLGA microparticles exhibit a slower release profile, with a significant less cumulative release over 28 days,

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less than 20%, 30% and 55% respectively, than the 25% TCA PLGA depot exemplified in Example 4. The 40% TCA containing depot exhibits a faster release profile, with greater than 80% of the triamcinolone released by day 7 with a similar total cumulative release, than the 25% TCA PLGA depot exemplified in Example 4.

Influence of Molecular Weight on TCA PLGA 75:25 Microparticle Formulations:

In another microparticle formulation, triamcinolone acetonide was incorporated in PLGA of the same lactide to glycolide molar ratio as cited in Example 4 but of a lower molecular weight. Low molecular weight PLGA is known to allow for more complete and faster release of pharmaceutical agents incorporated into microparticles than their higher molecular weight counterparts. (Anderson et al. "Biodegradation and biocompatibility of PLA and PLGA microspheres." *Advanced Drug Delivery Reviews* 28 (1997): 5-24; Bouissou et al., "Poly(lactic-co-glycolic acid) Microspheres." *Polymer in Drug Delivery* (2006): Chapter 7).

250 mg of triamcinolone acetonide and 750 mg of PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.27 dL/g and molecular weight of 29 kDa) were dispersed in 14.25 grams of dichloromethane. The dispersion was atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 µm sieve.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Malvern Mastersizer 2000) by dispersing a 250 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. Sonication was maintained as the sample was stirred at 2500 rpm and measurements taken every 15 seconds, with the average of three measurements reported. 10 mg of TCA containing microparticles were added to 10 mL of dimethylsulfoxide (DMSO), mixed until dissolved and an aliquot analyzed by HPLC to determine the microparticle drug load. Another 4 mg of TCA containing microparticles were suspended in 20 mL of phosphate buffered saline (PBS) containing 0.5% sodium dodecyl sulfate (SDS) maintained at 37° C. 0.5 mL of the media was removed at regular intervals, replaced at each interval with an equivalent amount of fresh media to maintain a constant volume, and analyzed by HPLC to determine microparticle in vitro release. Analysis by HPLC was conducted using a C18 (Waters Nova-Pack C-18, 3.9×150 mm) and 35% acetonitrile mobile phase at 1 ml/min flow rate with UV detection at 240 nm. The results are shown in Table 9.

TABLE 9

Analytical Results of a Nominal 25% Triamcinolone Acetonide PLGA 75:25 (29 kDa) Microparticles				
PLGA(lactide: glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, µm)	In vitro release (%)
75:25	29.4	118	D0.1: 34.1 µm	0.2 day: 4.0
carboxylic			D0.5: 56.5 µm	1 day: 11.3
acid end-capped			D0.9: 95.2 µm	3 day: 22.5
0.27 dL/g				7 day: 35.9

TABLE 9-continued

Analytical Results of a Nominal 25% Triamcinolone Acetonide PLGA 75:25 (29 kDa) Microparticles				
PLGA(lactide: glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, µm)	In vitro release (%)
29 kDa				14 day: 48.3
25%				21 day: 53.4
				28 day: 56.5

In vitro cumulative release data is graphed in FIG. 18, along with the preferred formulation using a higher molecular PLGA 75:25. The use of lower molecular weight PLGA (29 kDa) did not improve the release of the triamcinolone acetonide from the microparticles as expected, in fact the rate of release decreased and the release was incomplete as compared to higher molecular weight PLGA (PLGA, 54 kDa).

In another formulation of low molecular weight PLGA 75:25(29 kDa), polyethylene glycol, 10% PEG 3350, was added while maintaining the same amount of triamcinolone acetonide. As shown with other PEG containing formulations, there was no impact of this additive on the cumulative percent in vitro release profile as compared to the formulation not containing PEG (data not shown).

Influence of PLGA Lactide to Glycolide Ratio:

In other triamcinolone acetonide microparticle formulations, PLGA of equimolar lactide to glycolide ratio were employed instead of PLGA (75:25). PLGA (50:50) is known to allow for faster degradation and release of pharmaceutical agents incorporated into microparticles than PLGA's with greater lactide versus glycolide content (Anderson et al. "Biodegradation and biocompatibility of PLA and PLGA microspheres." *Advanced Drug Delivery Reviews* 28 (1997): 5-24; Bouissou et al., "Poly(lactic-co-glycolic acid) Microspheres." *Polymer in Drug Delivery* (2006): Chapter 7). Multiple formulations using PLGA 50:50 with differing amounts of triamcinolone acetonide, with and without PEG, different PLGA molecular weights and different PLGA endcaps were exemplified.

Formulations were prepared with 200 mg, 250 mg, 300 mg and 350 mg of triamcinolone acetonide and corresponding amount of PLGA (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.48 dL/g and molecular weight of 66 kDa) to yield 1000 mg total solids were dispersed into a quantity of dichloromethane to achieve a 5% PLGA solution. In another iteration, 300 mg of triamcinolone acetonide, 100 mg of polyethylene glycol (PEG 3350) and 650 mg of PLGA (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.48 dL/g and molecular weight of 66 kDa) were dispersed in 14.25 grams of dichloromethane. In another iteration, 300 mg of triamcinolone acetonide and 700 mg of PLGA (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.18 dL/g and molecular weight of 18 kDa) to yield 1000 mg total solids were dispersed in 14.25 grams of dichloromethane. The dispersions were atomized into micro-droplets by adding the dispersion to the feed well of a rotating disk, rotating at a speed of approximately 3300 rpm inside a temperature controlled chamber maintained at 38-45° C. The solvent was evaporated to produce solid microparticles. The microparticles were collected using a cyclone separator and, subsequently, sieved through a 150 µm sieve.

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Particle size of the TCA incorporated microparticles was determined using laser diffraction (Malvern Mastersizer 2000) by dispersing a 250 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. Sonication was maintained as the sample was stirred at 2500 rpm and measurements taken every 15 seconds, with the average of three measurements reported. 10 mg of TCA containing microparticles were added to 10 mL of dimethylsulfoxide (DMSO), mixed until dissolved and an aliquot analyzed by HPLC to determine the microparticle drug load. Another 4 mg of TCA containing microparticles were suspended in 20 mL of phosphate buffered saline (PBS) containing 0.5% sodium dodecyl sulfate (SDS) maintained at 37° C. 0.5 mL of the media was removed at regular intervals, replaced at each interval with an equivalent amount of fresh media to maintain a constant volume, and analyzed by HPLC to determine microparticle in vitro release. Analysis by HPLC was conducted using a C18 (Waters Nova-Pack C-18, 3.9x 150 mm) and 35% acetonitrile mobile phase at 1 ml/min flow rate with UV detection at 240 nm. The results are shown in Table 10.

TABLE 10

Analytical Results of Triamcinolone Acetonide PLGA 50:50 Microparticle Formulations				
PLGA(lactide: glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 20% TCA	19.2	96	D0.1: 30.0 μm D0.5: 48.5 μm D0.9: 77.0 μm	0.2 day: 2.1 1 day: 3.3 3 day: 17.0 7 day: 18.7 14 day: 21.0 21 day: 23.5 28 day: 25.6
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 25% TCA	23.9	95.6	D0.1: 30.2 μm D0.5: 48.2 μm D0.9: 75.8 μm	0.2 day: 4.0 1 day: 7.8 3 day: 21.1 7 day: 32.1 14 day: 39.2 21 day: 40.0 28 day: 40.8
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 30% TCA	29.3	97.6	D0.1: 31.5 μm D0.5: 48.0 μm D0.9: 68.9 μm	0.2 day: 5.1 1 day: 16.0 3 day: 33.6 7 day: 49.9 14 day: 54.0 21 day: 53.2 28 day: 52.2
50:50 carboxylic acid end-capped 0.18 dL/g 18 kDa 30% TCA	27.2	91	D0.1: 37.6 μm D0.5: 59.8 μm D0.9: 93.9 μm	0.2 day: 4.4 1 day: 9.8 3 day: 13.8 7 day: 17.7 14 day: 21.9 21 day: 26.3 28 day: 36.6
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 30% TCA 10% PEG 3350	30.4	101	D0.1: 38.1 μm D0.5: 56.6 μm D0.9: 82.1 μm	0.2 day: 4.2 1 day: 14.6 3 day: 32.2 7 day: 51.0 14 day: 60.1 21 day: 61.1 28 day: 60.1

TABLE 10-continued

Analytical Results of Triamcinolone Acetonide PLGA 50:50 Microparticle Formulations				
PLGA(lactide: glycolide molar ratio ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
50:50 carboxylic acid end-capped 0.48 dL/g 66 kDa 35% TCA	34.4	98.3	D0.1: 35.1 μm D0.5: 52.3 μm D0.9: 75.6 μm	0.2 day: 7.1 1 day: 23.3 3 day: 47.6 7 day: 66.9 14 day: 69.3 21 day: 68.3 28 day: 66.7
50:50 ester endcapped 0.4 dL/g 66 kDa 25% TCA	23.2	93	D0.1: 34.2 μm D0.5: 51.7 μm D0.9: 77.4 μm	0.2 day: 3.1 1 day: 7.8 3 day: 12.5 7 day: 15.4 14 day: 16.2 21 day: 16.0 28 day: 16.4

In-vitro release profiles of the various PLGA (50:50) formulations are shown in the FIG. 19. The use of PLGA (50:50) did not improve the release kinetics of the triamcinolone acetonide as compared to the PLGA (75:25). Unexpectedly, 25% triamcinolone acetonide microparticles in PLGA (50:50) release the corticosteroid at a slower rate and give an incomplete release as compared to the equivalent amount of triamcinolone acetonide incorporated in PLGA 75:25. All the PLGA 50:50 formulation show a substantial lag phase, where little or any TCA is being released after 7 days, which continues to about day 50. As observed with TCA PLGA 75:25 formulations, increasing the amount of TCA increases the rate of release and allows for more TCA to be released before entering the lag phase. Similarly, the addition of PEG has minimal influence on the release rate of TCA, while lower molecular weight PLGA 50:50 decrease the release rate as observed with PLGA 75:25 formulations.

Based on the studies described herein, the Class B corticosteroid microparticle formulations, for example, the TCA microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 22%-28% of the microparticle; and (ii) the polymer is PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.3 to 0.5 dL/g, and or having a lactide:glycolide molar ratio of 80:20 to 60:40.

Example 5

Preparation of Triamcinolone Acetonide PLGA
Microparticles by Solid in Oil in Water (S/O/W)
Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, triamcinolone acetonide (TCA, 9α-Fluoro-11β,16α,17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione 16,17-acetonide; 9α-Fluoro-16α-hydroxyprednisolone 16α,17α-acetonide) incorporated into microparticles.

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Formulations were prepared by dissolving approximately 1 gram of PLGA in 6.67 mL of dichloromethane (DCM). To the polymer solution, 400 mg of triamcinolone acetonide was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to rotate at approximately 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer) added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the TCA incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 ml glass vials in 8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 µm; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 µm, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm.

In one group of suitable thirty day formulations, the PLGA is an ester end capped PLGA (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.71 dL/g and molecular weight of 114 kDa) with 10% or 20% triblock (TB) polymer (PLGA-PEG-PLGA). Triblock polymer was synthesized using a method described by Zentner et al 2001 (Zentner et al. "Biodegradable block copolymers for delivery of proteins and water-insoluble drugs." *J Control Release* 72 (2001): 203-15) and refined by Hou et al 2008 (Hou et al., "In situ gelling hydrogels incorporating microparticles as drug delivery carriers for regenerative medicine." *J Pharm Sci* 97(9) (2008): 3972-80). It is synthesized using a ring opening polymerization of cyclic dimmers of D,L-lactide and glycolide with PEG 1,500 kDa in the presence of stannous octoate. In vitro release (lactide:glycolide molar ratio of 50:50, inherent viscosity of 0.40 dL/g and molecular weight of 66 kDa). The analytical results for these formulations are shown in Table 11.

TABLE 11

Analytical Results of Nominal 28.6% Triamcinolone Acetonide in PLGA 75:25 plus Triblock Microparticle Formulations					
PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% TCA by weight)	Incor-poration effi-ciency (%)	Particle size (Dv, µm)	In vitro release (%)	
5 10 15 20 25 30	23.8	83.2	D0.1: 38.9 µm D0.5: 74.7 µm D0.9: 103.0 µm	1 day: 8.2	
				2 day: 14.2	
				3 day: 15.7	
				4 day: 18.2	
				6 day: 28.8	
				9 day: 38.9	
				12 day: 49.8	
				16 day: 61.6	
				20 day: 66.4	
				24 day: 68.7	
				30 day: 72.3	
				35 day: 72.8	
	24.8	86.7	D0.1: 39.5 µm D0.5: 74.6 µm D0.9: 104.2 µm	1 day: 5.5	
				2 day: 8.9	
				3 day: 12.8	
				4 day: 14.5	
				6 day: 28.4	
				9 day: 35.6	
				12 day: 47.8	
				16 day: 53.0	
				20 day: 64.3	
				24 day: 67.3	
				30 day: 73.0	
				35 day: 73.0	

The in vitro cumulative release profiles for both triblock containing formulations are shown in FIG. 20. The amount of triblock in the tested formulations did not influence the cumulative percent release.

In one iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. These calculated doses equal 149 mg of microparticles containing 35 mg of TCA and 252 microparticles containing 62 mg of TCA, for the 10% and 20% triblock formulations respectively (FIG. 21 and FIG. 22). In a second iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would not have an suppress the HPA axis, i.e. endogenous cortisol suppression more than 35%. These calculated doses equal 66 mg of microparticles containing 16 mg of TCA and 47 microparticles containing 12 mg of TCA, for the 10% and 20% triblock formulations respectively (FIG. 23 and FIG. 24).

In another suitable formulation lasting greater than 30 days and up to 90 days, the PLGA polymer consists of two different molecular weight PLGA 75:25 polymers in a two to one ratio, PLGA 75:25 (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.27 dL/g and molecular weight of 29 kDa) and ester end capped PLGA 5.5E (lactide:glycolide molar ratio of 75:25, inherent viscosity of 0.58 dL/g and molecular weight of 86 kDa), respectively. The formulation was processed as described above with the exception that 200 mg of triamcinolone acetonide was used in the formulation instead of 400 mg and similarly analyzed as describe for other formulations. The results are shown in the Table 12.

TABLE 12

Analytical Results of a Nominal 16.7% Triamcinolone Acetonide in Mixed Molecular Weight PLGA 75:25 Microparticle Formulation				
PLGA (lactide: glycolide molar ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (%) TCA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μm)	In vitro release (%)
75:25 ester endcapped	14.6	87.7	D0.1: 36.5 μm	1 day: 12.4
0.58 dL/g			D0.5: 54.0 μm	2 day: 21.6
86 kDa			D0.9: 69.4 μm	3 day: 27.3
And				4 day: 33.6
75:25				6 day: 41.2
carboxylic acid end-capped				9 day: 50.7
0.27 dL/g				12 day: 54.3
29 kDa				17 day: 62.0
16.7% TCA				20 day: 73.1
				25 day: 75.5
				30 day: 82.9
				35 day: 84.6
				42 day: 87.4
				49 day: 89.2

In Vitro Cumulative Percent TCA Release Data is Graphed in FIG. 25.

In one iteration of these in vitro release data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. This calculated dose equals 317 mg of microparticles containing 46 mg of TCA. In a second iteration of these data, the amount of TCA released per day was calculated based on a human dose, as exemplified in Table 2, that would not have an suppress the HPA axis, i.e. endogenous cortisol suppression more than 35%. This calculated dose equals 93 mg of microparticles containing 14 mg of TCA.

Several other triamcinolone acetonide PLGA depots were formulated in the same manner as described above with different polymers including polycaprolactone (14 kDa), PLGA 50:50 (carboxylic acid end-capped, 0.44 dL/g, MW 56 kDa), PLGA 85:15 (carboxylic acid end-capped, 0.43 dL/g, 56 kDa) and a mixed molecular weight formulation using PLGA 75:25 (carboxylic acid end capped, 0.27 dL/g, MW 29 kDa) and PLGA 75:25 (ester end-capped, 0.57 dL/g, MW 86 kDa) in a two to one ratio. The in vitro cumulative percent release of triamcinolone acetonide is shown in FIG. 28. None of these formulations were suitable for a nominal thirty day or longer duration pharmaceutical depot. Polycaprolactone release all the triamcinolone acetonide prior to 14 days. The PLGA 50:50 microparticles released about 35% of its content by day 12 and then entered a lag phase where no drug was released up to 30 days. The PLGA 85:15 microparticles exhibited similar in vitro release kinetics as the PLGA 50:50, releasing about 30% of its content by day 12 and then entered a lag phase where no drug was released up to 30 days (See FIG. 28). A similar phenomenon is seen as shown in Example 4, where the mixed molecular weight PLGA 75:25 unexpectedly exhibits faster initial release of the triamcinolone acetonide than PLGA 50:50.

Based on the studies described herein, the Class B corticosteroid microparticle formulations, for example, the TCA microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 12%-28% of the microparticle; and (ii) the

polymer is (1) PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.3 to 0.5 dL/g, containing 10%-20% Triblock and/or having a lactide:glycolide molar ratio of 80:20 to 60:40 or (2) a mixture of low and high molecular weight PLGAs in a two to one ratio. The low molecular weight PLGA has a molecular weight of range of 15-35 kDa and an inherent viscosity range from 0.2 to 0.35 dL/g, and the high molecular weight PLGA has a range of 70-95 kDa and an inherent viscosity range of 0.5 to 0.70 dL/g.

Example 6

Preparation of Prednisolone PLGA Microparticles by Solid in Oil in Water (S/O/W) Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, prednisolone (PRED, 11β,17,21-trihydroxy-pregna-1,4-diene-3,20-dione) incorporated into microparticles in PLGA 50:50.

Formulations were prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.44 dL/g, MW 56 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 400 mg of prednisolone was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer) added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the PRED incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 ml glass vials in 8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μm; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μm, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm. The analytical results are shown in the Table 13.

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TABLE 13

Analytical Results of a Nominal 28.6% Prednisolone in PLGA 50:50 Microparticle Formulation				
PLGA(lactide: glycolide molar ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% PRED by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μ m)	In vitro release (%)
50:50	19.0	66.4	D0.1: 34.4 μ m	1 day: 7.2
carboxylic			D0.5: 66.9 μ m	2 day: 11.5
acid end-capped			D0.9: 87.5 μ m	3 day: 15.6
0.44 dL/g				4 day: 20.2
56 kDa				5 day: 24.0
28.6% PRED				6 day: 28.4
				7 day: 32.7
				9 day: 36.5
				11 day: 41.4
				13 day: 45.0
				15 day: 49.3
				18 day: 52.0
				21 day: 55.2
				24 day: 58.3
				27 day: 62.3
				30 day: 65.9

In vitro release profile of the prednisolone PLGA microparticles is shown in FIG. 29. This formulation is suitable for a 30 day formulation or greater.

In one iteration of the cumulative percent in vitro release data, the amount of prednisolone released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35% (FIG. 30). The calculated dose equals 699 mg of microparticles containing 133 mg of PRED. In a second iteration of these data, the amount of PRED released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression of less than 35% (FIG. 31). This calculated dose equals 377 mg of microparticles containing 72 mg of PRED.

Based on the studies described herein, the Class A corticosteroid microparticle formulations, for example, the prednisolone microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 10%-40% of the microparticle, for example, between 15%-30% of the microparticle; and (ii) the polymer is PLGA having a molecular weight in the range of about 45 to 75 kDa, having an inherent viscosity in the range of 0.35 to 0.5 dL/g, and or having a lactide:glycolide molar ratio of 60:40 to 45:55.

Example 7

Preparation of Betamethasone PLGA Microparticles
by Solid in Oil in Water (S/O/W) Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, betamethasone (BETA, 9-Fluoro-11 β ,17,21-trihydroxy-16 β -methylpregna-1,4-diene-3,20-dione) incorporated into microparticles in PLGA 50:50.

A formulation was prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.44 dL/g, MW 56 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 400 mg of betamethasone was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL

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of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer) added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the BETA incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 mL HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 mL glass vials in 8-20 mL of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 mL of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μ m; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μ L, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 mL/min, with detection at a wavelength of 254 nm. The analytical characteristics of the betamethasone PLGA microparticles are shown in the Table 14.

TABLE 14

Analytical Results of a Nominal 28.6% Betamethasone PLGA 50:50 Microparticle Formulation				
PLGA(lactide: glycolide molar ratio/inherent viscosity/molecular weight/target % TCA/% PEG	Drug load (% BETA by weight)	Incor- poration effi- ciency (%)	Particle size (Dv, μ m)	In vitro release (%)
50:50	22.8	79.7	D0.1: 42.1 μ m	1 day: 2.0
carboxylic			D0.5: 71.7 μ m	2 day: 3.1
acid endcapped			D0.9: 102.7 μ m	3 day: 4.8
0.44 dL/g				4 day: 7.7
56 kDa				5 day: 12.5
28.6% BETA				6 day: 21.4
				7 day: 30.8
				9 day: 38.6
				11 day: 43.9
				13 day: 49.6
				15 day: 55.5
				18 day: 57.5
				21 day: 59.2
				24 day: 60.8
				27 day: 62.9
				30 day: 72.4

In vitro release profile of the betamethasone PLGA micro-particles is shown in FIG. 32. This formulation is suitable for a 30 day formulation or greater.

In one iteration of the in vitro release data, the amount of betamethasone released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. This calculated dose equals 111 mg of microparticles containing 25 mg of betamethasone. In a second iteration of these data, the amount of betamethasone released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the IIPA axis, i.e. endogenous cortisol suppression never exceeding 35%. This calculated dose equals 38 mg of microparticles containing 9 mg of betamethasone. These doses are both graphically represented in FIGS. 33 and 34.

Based on the studies described herein, the Class C corticosteroid microparticle formulations, for example, the betamethasone microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 10%-40% of the microparticle, for example, between 15%-30% of the microparticle; and (ii) the polymer is PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.35 to 0.5 dL/g, and/or having a lactide:glycolide molar ratio of 60:40 to 45:55.

Example 8

Preparation of Fluticasone Propionate PLGA Microparticles by Solid in Oil in Water (S/O/W) Emulsion

A pharmaceutical depot was prepared comprised of the corticosteroid, fluticasone propionate (FLUT, S-(fluoromethyl) 6 α ,9-difluoro-11 β ,17-dihydroxy-16 α -methyl-3-oxoandrost-1,4-diene-17 β -carbothioate, 17-propionate) incorporated into microparticles in PLGA 50:50.

A formulation was prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.45 dL/g, molecular weight 66 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 200 mg of fluticasone propionate was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the FLUT incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 mL HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle

samples, nominally 1 g were placed in 22 ml glass vials in 8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μ m; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μ m, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm. The analytical results of the fluticasone propionate PLGA microparticles are shown in Table 15.

TABLE 15

Analytical Results of a Nominal 16.7% Fluticasone PLGA 50:50 Microparticle Formulation				
PLGA(lactide:glycolide molar ratio ratio/inherent viscosity/molecular weight/target % FLUT/	Drug load (% FLUT by weight)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)
50:50	8.5	51.1	D0.1: 34.1 μ m	1 day: 29.5
carboxylic acid endcapped			D0.5: 65.5 μ m	2 day: 43.5
0.45 dL/g			D0.9: 95.0 μ m	3 day: 46.7
66 kDa				4 day: 50.9
16.7% FLUT				5 day: 55.5
				6 day: 58.6
				7 day: 60.1
				9 day: 63
				11 day: 66.8
				13 day: 67.8
				15 day: 68.7
				18 day: 73.7
				21 day: 81.8
				24 day: 93.7
				26 day: 97.1
				31 day: 100.8

In vitro release profile of the fluticasone propionate PLGA microparticles is shown in FIG. 35. This formulation is suitable for a 30 day formulation or greater.

In one iteration of the in vitro release data, the amount of fluticasone propionate released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. This calculated dose equals 178 mg of microparticles containing 15 mg of fluticasone propionate. In a second iteration of these data, the amount of fluticasone propionate released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35%. This calculated dose equals 24 mg of microparticles containing 2 mg of fluticasone propionate. These doses are both graphically represented in FIGS. 36 and 37.

Other fluticasone propionate PLGA depots were formulated in the same manner as described above with different PLGA polymers or amounts fluticasone propionate. In one formulation, a PLGA polymer with a higher lactide to gly-

colide ratio (PLGA 75:25 (ester end-capped PLGA 75:25, lactide:glycolide molar ratio of 75:25, 0.58 dL/g, MW 86 kDa) was used instead of the PLGA 50:50 as previously described. Unlike the triamcinolone acetone preparations described in Example 5, but typically expected as described in the literature, the higher lactide to glycolide ratio resulted in a slower release, where 30% release in 14 days, followed by a substantial lag phase where little drug is released for a minimum of thirty days. In another example, 400 mg of fluticasone propionate instead of 200 mg was used in preparation of PLGA 50:50 microparticles (target drug load 28.6%). Unlike triamcinolone acetone microparticle preparations, the higher drug load did not result in a significantly different release of fluticasone propionate; FIG. 38 shows the in vitro release of all three fluticasone propionate formulations.

Based on the studies described herein, the Class D corticosteroid microparticle formulations, for example, the fluticasone or fluticasone propionate microparticle formulations, exhibiting the desired release kinetics have the following characteristics: (i) the corticosteroid is between 8%-20% of the microparticle, and (ii) the polymer is PLGA having a molecular weight in the range of about 40 to 70 kDa, having an inherent viscosity in the range of 0.35 to 0.5 dL/g, and or having a lactide:glycolide molar ratio of 60:40 to 45:55.

Example 9

Preparation of Dexamethasone Microparticles by Solvent Dispersion in PLGA

A pharmaceutical depot was prepared comprised of the corticosteroid, dexamethasone (DEX, 9-Fluoro-11 β ,17,21-trihydroxy-16 α -methylpregna-1,4-diene-3,20-dione) incorporated into microparticles in PLGA 50:50.

A formulation was prepared by dissolving approximately 1 gram of PLGA 50:50 (lactide:glycolide molar ratio of 50:50, inherent viscosity 0.45 dL/g, molecular weight 66 kDa) in 6.67 mL of dichloromethane (DCM). To the polymer solution, 200 mg of dexamethasone was added and sonicated. Subsequently, the corticosteroid containing dispersion was poured into 200 mL of 0.3% polyvinyl alcohol (PVA) solution while homogenizing with a Silverson homogenizer using a rotor fixed with a Silverson Square Hole High Shear Screen™, set to spin at 2,000 rpm to form the microparticles. After two minutes, the beaker was removed, and a glass magnetic stirrer added to the beaker, which was then placed onto a multi-way magnetic stirrer and stirred for four hours at 300 rpm to evaporate the DCM. The microparticles were then washed with 2 liters of distilled water, sieved through a 100 micron screen. The microparticles were then lyophilized for greater than 96 hours and vacuum packed.

Particle size of the DEX incorporated microparticles was determined using laser diffraction (Beckman Coulter LS 230) by dispersing a 50 mg aliquot in water, with the refractive index (RI) for water and PLGA, set at 1.33 and 1.46 respectively. The sample was stirred at the particle size measurement measurements taken and the results reported. Drug load was determined by suspending a nominal 10 mg of microparticles in 8 ml HPLC grade methanol and sonicating for 2 hours. Samples were then centrifuged at 14,000 g for 15 mins before an aliquot of the supernatant was assayed via HPLC as described below. Corticosteroid-loaded microparticle samples, nominally 1 g were placed in 22 ml glass vials in

8-20 ml of 0.5% v/v Tween 20 in 100 mM phosphate buffered saline and stored in a 37° C. incubator with magnetic stirring at 130 rpm. Each test sample was prepared and analyzed in duplicate to monitor possible variability. At each time point in the release study, microparticles were allowed to settle, and an aliquot of between 4-16 ml of supernatant were taken, and replaced with an equal volume of fresh 0.5% v/v Tween 20 in 100 mM phosphate buffered saline. Drug load and in vitro release samples were analyzed by HPLC using a Hypersil C18 column (100 mm, i.d. 5 mm, particle size 5 μ m; ThermoFisher) and Beckman HPLC. All samples were run using a sample injection volume of 5 μ m, and column temperature of 40° C. An isocratic mobile phase of 60% methanol and 40% water was used at a flow rate of 1 ml/min, with detection at a wavelength of 254 nm. The analytical results for the dexamethasone PLGA microparticles are shown in Table 16.

TABLE 16

Analytical Results of a Nominal 28.6% Dexamethasone PLGA 50:50 Microparticle Formulation

PLGA(lactide:glycolide molar ratio/inherent viscosity/molecular weight/target % FLUT/	Drug load (% DEX by weight)	Incorporation efficiency (%)	Particle size (Dv, μ m)	In vitro release (%)
50:50	22.1	77.2	D0.1: 41.2 μ m	1 day: 2.9
carboxylic acid endcapped			D0.5: 71.9 μ m	2 day: 4.6
0.45 dL/g			D0.9: 99.1 μ m	3 day: 6.3
66 kDa				4 day: 8.7
28.6% DEX				5 day: 10.9
				6 day: 12.7
				7 day: 15.0
				9 day: 16.4
				11 day: 18.0
				13 day: 20.7
				15 day: 24.6
				18 day: 26.2
				21 day: 28.1
				24 day: 30.3
				27 day: 34.0
				30 day: 46.3

In vitro cumulative percent release of the dexamethasone is shown in 39, and results in suitable formulation for a minimum of thirty days and, assuming linear release, likely up to 60 days.

In one iteration of the in vitro release data, the amount of dexamethasone released per day was calculated based on a human dose, as exemplified in Table 2, which may achieve a temporary suppression of endogenous cortisol (greater than 50%) and, within 14 days, achieve cortisol suppression of endogenous cortisol of less than 35%. In a second iteration of these data, the amount of dexamethasone released per day was calculated based on a human dose, as exemplified in Table 2 that would not suppress the HPA axis, i.e. endogenous cortisol suppression never exceeding 35%. In the case of dexamethasone, where the data is truncated, both calculated human doses are the same; 36 mg of microparticles containing 8 mg of dexamethasone. The doses are graphically represented in FIG. 40.

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Pharmacology, Pharmacokinetics and Exploratory
Safety Study of Corticosteroid Formulations

In an exploratory safety study in rats, single intra-articular (IA) doses of TCA immediate release (TCA IR) (0.18 and 1.125 mg) and doses of TCA in 75:25 PLGA formulation microparticles (FX006) (0.28, 0.56 and 1.125 mg (i.e., the maximum feasible dose) of TCA) were evaluated. Blood samples were collected at various time points for determination of plasma concentrations. Plasma concentration-time data from this study and pharmacokinetic (PK) analysis thereof are shown in FIGS. 41-43 and Tables 17-20.

As seen in FIGS. 41A-41D, FX006 dosed at 1.125 mg resulted in a very slow absorption of TCA in the systemic circulation and a markedly lower C_{max} as compared to TCA IR.

As shown in Table 17, the mean AUC_{0-24} values of TCA following 1.125 mg administration of FX006 were 2.1-fold lower than those observed for TCA IR (i.e., 2856 vs. 6065 ng·h/mL, respectively). The mean C_{max} values of TCA following 1.125 mg administration of FX006 were 15-fold lower than those observed for TCA IR (i.e., 125 vs. 8.15 ng/mL, respectively). The absorption of TCA following administration of FX006 was slower than that observed for TCA IR, with mean T_{max} values observed at 3.33 and 1.00 h, respectively. The elimination half-life of TCA following administration of 1.125 mg FX006 and TCA IR were 451 and 107 h, respectively.

TABLE 17

Summary of TCA Plasma Pharmacokinetic Parameters										
Variable	Treatment									
	FX006 (0.28 mg)		FX006 (0.56 mg)		FX006 (1.125 mg)		TCA IR (0.18 mg)		TCA IR (1.125 mg)	
	Mean	(CV %)	Mean	(CV %)	Mean	(CV %)	Mean	(CV %)	Mean	(CV %)
AUC_{0-24} (ng · h/mL)	31.0	(76.0)	33.0	(19.1)	136	(6.0)	297	(21.5)	1403	(13.2)
AUC_{0-24} (ng · h/mL)	356	(62.0)	572	(21.5)	2856	(17.2)	479	(32.6)	6065	(3.7)
AUC_{0-4} (ng · h/mL)	335	(66.5)	532	(23.8)	2142	(14.4)	456	(31.3)	6013	(3.4)
CL/F (mL/h)	1308	(96.6)	1014	(24.4)	403	(19.1)	400	(27.6)	186	(3.6)
C_{max} (ng/mL)	1.82	(66.2)	1.91	(10.2)	8.15	(12.5)	41.6	(25.1)	125	(5.3)
$T_{1/2}$ (h)	99.5	(39.9)	180	(27.0)	451	(20.8)	35.6	(63.5)	107	(56.7)
T_{max} (h)	17.7	(148.9)	16.7	(162.8)	3.33	(69.3)	2.00	(0.0)	1.00	(0.0)
$V_{d/F}$ (mL)	274215	(117.0)	326966	(30.2)	240481	(17.7)	12069	(53.4)	23829	(34.4)

The above results suggest a slower distribution and bioavailability of TCA in the systemic circulation following administration of FX006 as compared to TCA IR. Without wishing to be bound by theory, the slower distribution FX006 into the systemic circulation may be related to the longer residence time of FX006 at the site of injection. This is supported by the lesser availability of the FX006 microparticle formulation in the early "burst" phase, where only 4-9% of product is released, compared to at least 23% of the IR product.

Bioavailability of TCA in the systemic circulation following administration of FX006 was 3-fold lower than that observed for TCA IR, as shown in Table 18.

TABLE 18

Bioavailability of TCA in Plasma		
Absolute Bioavailability Comparison		
	FX006 (0.28 mg)	TCA IR (0.18 mg)
F_{abs} (%)	17.9	58.6

For the 0.56 and 1.125 mg dose levels of FX006, apparent F % were 23.1% and 58.1%, respectively. The IV data in rats shown in Table 19 was used as a reference to calculate F .

TABLE 19

Pharmacokinetic Parameters of TCA in Rat Plasma After i.v. (50 mg/kg bolus + 23 mg/kg/h Infusion) Administration of Triamcinolone Acetonide Phosphate				
Parameter	Rat 1	Rat 2	Rat 3	Mean ± SD
V_z (L/kg)	0.684	0.856	1.29	0.944 ± 0.314
CL (L/h/kg)	1.15	0.790	0.872	0.937 ± 0.188
k_{12} (h ⁻¹)	1.64	1.79	1.59	1.67 ± 0.102
k_{21} (h ⁻¹)	1.04	0.640	1.13	0.937 ± 0.261

TABLE 19-continued

Pharmacokinetic Parameters of TCA in Rat Plasma After i.v. (50 mg/kg bolus + 23 mg/kg/h Infusion) Administration of Triamcinolone Acetonide Phosphate				
Parameter	Rat 1	Rat 2	Rat 3	Mean ± SD
$T_{1/2}$ (h)	1.55	3.71	2.87	2.71 ± 1.09
f_u	0.084	0.110	0.085	0.093 ± 0.015

from Rojas et al., "Microdialysis of triamcinolone acetonide in rat muscle." *J Pharm Sci* 92(2) (2003): 394-397.

The initial “burst” (i.e., exposure up to 24 h) accounted for less than 10% of the total systemic exposure of FX006. The initial burst accounted for ~23-62% of the total exposure for the TCA IR product, as shown in Table 20.

TABLE 20

Variable	Relative Availability of TCA in Plasma (Initial Burst vs. Delayed Release)				
	Treatment				
	FX006 (0.28 mg) Mean	FX006 (0.56 mg) Mean	FX006 (1.125 mg) Mean	TCA IR (0.18 mg) Mean	TCA IR (1.125 mg) Mean
AUC ₀₋₂₄ (ng · h/mL)	31.0	33.0	136	297	1403
AUC _{0-∞} (ng · h/mL)	356	572	2856	479	6065
AUC _{24-∞} (ng · h/mL)	325	539	2720	182	4662
% Initial Burst	8.69	5.76	4.76	62.1	23.1

In this same study, groups of animals were sacrificed 28 days after dosing, and the remaining were terminated on Day 42. Body weights were monitored throughout the study and key organs (spleen, adrenal glands, thymus) were weighed upon necropsy. The injected knee and the contralateral control joints were prepared for histological assessment. Toluidine blue stained sections of joints were evaluated for treatment-related alterations. Histologic changes were described, wherever possible, according to their distribution, severity, and morphologic character.

Histological analysis demonstrated the following observations. First, injected joints from placebo (blank PLGA microspheres)-treated animals had minimal multifocal macrophage infiltration in associated with 20-130 μm diameter microspheres, whereas none of the active FX006-injected joints showed the presence of any microspheres at Day 28. Placebo-treated rat joints had no cartilage or joint changes save for the presence of spontaneous cartilage cysts in a few joints (1 at Day 28, 2 at Day 42) in the right (injected) knees. The left knees in the placebo-treated rat joints were normal. In comparison, both knees in the high dose TCA IR and the high and mid-dose FX006-groups showed some mild bone marrow hypocellularity and growth plate atrophy (dose dependent for FX006). Both knees in the low dose TCA IR and FX006 animals were normal. Spontaneous cartilage cysts noted in placebo animals were also noted in all groups dosed with FX006 with no increase in incidence or severity. High dose TCA IR increased cartilage cysts at Day 42 but not at Day 28. In general, FX006-treated animals had normal articular cartilage despite the presence of catabolic effects on other joint structures, which was likely more readily observed on account of the young age of the animals.

Overall, all observed effects of FX006, especially at the high dose, such as body weight loss and reduced organ weights were also seen with TCA IR. The time course of inhibition of the HPA axis (measured as corticosterone levels) is shown in FIG. 42. It should be noted that at the lowest dose of FX006 (0.28 mg; circles) corticosterone levels were initially inhibited but recovered back to near baseline by Day 14 post-dose. Similarly, with TCA IR at the lowest dose (0.18 mg), corticosterone levels recovered by Day 7 (squares). With the mid (0.56 mg) and high (1.125 mg) doses of FX006 and the high dose of TCA IR (1.125 mg), corticosterone levels were inhibited longer as shown in FIG. 42.

A PK-PD analysis demonstrated that inhibition of corticosterone was correlated with systemic TCA levels and followed a classical inhibitory model as shown in FIG. 43. The IC₅₀ was about 1 ng/mL and the E_{max} was achieved at 50-80 ng/mL.

Example 11

Evaluation of Efficacy of Single Doses of TCA Immediate Release and TCA Microparticle Formulation in Animal Model of Osteoarthritis

The studies described herein were designed to test and evaluate the efficacy of the corticosteroid microparticle formulations provided herein as compared to immediate release corticosteroid formulations. While the studies herein use TCA, it is understood that other corticosteroids, including other Class B corticosteroids, Class A corticosteroids, Class C corticosteroids, and Class D corticosteroids, can be evaluated using these materials, methods and animal models.

Efficacy of single intra-articular (IA) doses of FX006 (TCA in 75:25 PLGA formulation microparticles) and TCA IR (immediate release) was evaluated in a rat model of osteoarthritis of the knee via sensitization and challenge by peptidoglycan polysaccharide (PGPS). The model involves priming the animals with an intra-articular injection of PGPS in the right knee. The following day, any animals with no knee discomfort were eliminated from the test article groups and placed into the baseline group. Two weeks later, knee inflammation was reactivated by a tail vein injection of PGPS, 2.5 hr following IA dosing with FX006 or TCA IR at the doses selected (n=10/group). Differences in weight-bearing and gait (as a measure of joint pain experienced by the animals), histopathology, plasma PK etc. were evaluated.

Doses of FX006 (0.28, 0.12, 0.03 mg) and TCA IR (0.06, 0.03 mg) for this study were selected based on data from the study described above in Example 10 and an initial run of the PGPS model in which only TCA IR was evaluated at two IA dose levels. The goals of the present study were to demonstrate the following:

FX006 is efficacious at doses that do not inhibit the HPA axis

The duration of efficacy is a function of dose

FX006 provides more prolonged pain relief as compared to TCA IR—Since only about 10% of the TCA payload is expected to be released from FX006 in the first 24 hr, one TCA IR dose group (0.03 mg) was chosen to match 10% of the TCA in FX006 at a dose of 0.28 mg

Effects of matched doses of FX006 and TCA IR (0.03 mg)

The duration of efficacy was assessed by 3 different reactivations, 2 weeks apart. After that point, the arthritis observed in the animals becomes more wide-spread making the efficacy in the index knee more difficult to assess.

At the first reactivation, vehicle treated animals demonstrate painful gait as demonstrated by high pain scores (3.5 out of a maximum of 4 possible) as shown in FIGS. 44A, 44B, and 44C. FX006 at 0.28 mg (squares) showed good efficacy. In the previous study described in Example 10, this dose was demonstrated to inhibit the HPA axis immediately after dosing but a return to baseline function was demonstrated by Day 14. Interestingly, this dose of FX006 continued to be efficacious upon the 2nd and 3rd reactivations on Days 14 and 28 when the HPA axis function was presumably normal. It should also be noted that since HPA axis function returned to baseline by Day 7 at a 0.18 mg dose of TCA IR in the previous study described in Example 10, the effects of the doses of TCA IR used in the present study (0.06 and 0.03 mg) were

also in the presence of normal HPA axis function following an initial transient inhibition. Corticosterone measurements from the present study (as an indicator of HPA axis function) are presented as change from baseline for each treatment group in FIG. 46. As demonstrated from these data, corticosterone levels for all groups recovered by Day 14; hence the goal of prolonged efficacy with FX006 in the presence of normal HPA axis function was achieved.

Overall, a clear dose-dependence of response was noted for both FX006 and TCA IR. Also, if less than 10% of this dose is available by the day after dosing (Day 1), it should be noted in FIG. 44B that the efficacy of FX006 at 0.28 mg (squares) is greater than TCA IR at 0.03 mg (triangles) at all evaluations. Further, the duration of efficacy of TCA (both FX006 and IR) appears to be a function of dose, however, the prolonged release of TCA from the PLGA microspheres in FX006 results in more sustained efficacy. This is more clearly depicted in another representation of the data in FIG. 45 in which peak response for each dose as determined by gait/pain scores on Day 1 following each reactivation (Days 1, 15 and 29) are plotted. FIG. 46 plots the time course of corticosterone recovery for all study groups. On balance, across all groups that received the corticosteroid, there was recovery.

Plasma levels of TCA were measured in samples taken from all rats at baseline (Day -4), Days 0 (2 hr post dosing), 1, 3, 8, 14, 17, 21, 28, and 31. Concentration-time curves for all treatment groups are shown in FIG. 47A. FIG. 47B shows only the FX006 dose groups on a larger scale since maximal plasma concentrations with FX006 were far lower than those with TCA IR.

Histopathological evaluation of the knees taken from all animals at the end of the study (Day 32 at the end of the 3rd reactivation of arthritis) demonstrated statistically significant improvement by FX006 at the high and mid-range doses (0.28 and 0.12 mg) in the composite histological score and each component score (inflammation, pannus, cartilage damage and bone resorption) as shown in FIG. 48. As described above, the dose of 0.28 mg FX006 demonstrated strong efficacy (i.e. analgesic activity) throughout all 3 reactivations, whereas the dose of 0.12 mg was active but to a lesser degree through all 3 reactivations. At the doses of TCA IR used, the duration of efficacy was mostly through the first reactivation of arthritis, with partial efficacy of the higher (0.06 mg) dose in the second reactivation, and this also translated into a much smaller non-significant improvement in histological scores. Importantly, these data demonstrate that TCA has no deleterious effect on cartilage and as has been described in other settings, it actually reduces cartilage damage in an inflammatory milieu.

In conclusion, the prolonged residence of TCA in the joint upon IA dosing with FX006 resulted in extending the duration of efficacy in the rat PGPS model of arthritis with a significant histological improvement in inflammation, pannus formation, cartilage damage and bone resorption. FX006 had these effects without inhibiting HPA axis function as demonstrated by the return to baseline of corticosterone levels within 14 days after dosing. The clinical implications for the treatment of patients with osteoarthritis, rheumatoid arthritis and other inflammatory joint disorders are as follows:

Intra-articular injection of sustained release corticosteroid microparticle formulations provides prolonged pain relief relative to intra-articular injection of immediate release steroids.

Intra-articular injection of sustained release corticosteroid microparticle formulations is efficacious in reducing pain and inflammation at doses that do not inhibit the HPA axis.

The duration of efficacy of sustained release of intra-articular corticosteroid microparticle formulations is a function of dose.

Intra-articular injection of sustained release corticosteroid microparticle formulations slows, arrests, reverses, or otherwise inhibits structural damage to tissues caused by inflammation.

Although particular embodiments have been disclosed herein in detail, this has been done by way of example for purposes of illustration only, and is not intended to be limiting with respect to the scope of the appended claims, which follow. In particular, it is contemplated by the inventors that various substitutions, alterations, and modifications may be made to the invention without departing from the spirit and scope of the invention as defined by the claims. Other aspects, advantages, and modifications are considered to be within the scope of the following claims. The claims presented are representative of the inventions disclosed herein. Other, unclaimed inventions are also contemplated. Applicants reserve the right to pursue such inventions in later claims.

What is claimed is:

1. An injectable formulation comprising (a) controlled- or sustained-release microparticles comprising triamcinolone acetonide (TCA) or a pharmaceutically-acceptable salt thereof and a poly(lactic-co-glycolic) acid copolymer (PLGA) matrix, wherein the TCA comprises between 22% to 28% of the microparticles and wherein the PLGA has the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; and (ii) a lactic acid:glycolic acid molar ratio of 80:20 to 60:40, and wherein the TCA is released for between at least 14 days and 90 days upon administration to a joint.
2. The formulation of claim 1, wherein the PLGA copolymer has a molar ratio of lactic acid:glycolic acid of 75:25.
3. The formulation of claim 1, wherein the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle.
4. The formulation of claim 1, wherein the 22% to 28% of TCA in the microparticles comprises a total TCA load dose between 10 to 50 mg.
5. The formulation of claim 1, wherein the lactic acid-glycolic acid copolymer has an inherent viscosity in the range of 0.3 to 0.5 dL/g.
6. An injectable formulation comprising (a) controlled- or sustained-release microparticles comprising triamcinolone acetonide (TCA) or a pharmaceutically-acceptable salt thereof and a poly(lactic-co-glycolic) acid copolymer (PLGA) matrix, wherein the TCA comprises between 22% to 28% of the microparticles, wherein the microparticles have a mean diameter of between 10 μ m to 100 μ m, and wherein the PLGA has the following characteristics: (i) a molecular weight in the range of about 40 to 70 kDa; and (ii) a lactic acid:glycolic acid molar ratio of 80:20 to 60:40, wherein the TCA is released for between at least 14 days and 90 days upon administration to a joint.
7. The formulation of claim 6, wherein the PLGA copolymer has a molar ratio of lactic acid:glycolic acid of 75:25.
8. The formulation of claim 6, wherein the microparticles further comprise a polyethylene glycol (PEG) moiety, wherein the PEG moiety comprises between 25% to 0% weight percent of the microparticle.
9. The formulation of claim 6, wherein the 22 to 28% of TCA in the microparticles comprises a total TCA load dose between 10 to 50 mg.

49
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10. The formulation of claim 6, wherein the lactic acid-glycolic acid copolymer has an inherent viscosity in the range of 0.3 to 0.5 dL/g.

* * * * *

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Trial record 1 of 5 for: fx006 and osteoarthritis

Previous Study | Return to List | Next Study

Study of FX006 for the Treatment of Pain in Patients With Osteoarthritis of the Knee

This study is currently recruiting participants. (see Contacts and Locations)

Verified April 2015 by Flexion Therapeutics, Inc.

Sponsor:
Flexion Therapeutics, Inc.

Information provided by (Responsible Party):
Flexion Therapeutics, Inc.

ClinicalTrials.gov Identifier:
NCT02357459

First received: February 3, 2015
Last updated: April 10, 2015
Last verified: April 2015
History of Changes

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

Purpose

This study is a double-blind, randomized, single-dose study to assess the safety and efficacy of **FX006** for the treatment of pain in patients with **osteoarthritis** of the knee.

Approximately 450 patients with OA of the knee will be randomized to one of the three treatment groups (1:1:1) and treated with a single intra-articular (IA) injection of:

- 40 mg of **FX006**
- 40 mg of Triamcinolone Acetonide Injectable Suspension, USP (referred to as TCA IR in protocol)
- Normal Saline

Each patient will be evaluated for a total of 24 weeks following a single IA injection. Following screening, safety and efficacy will be evaluated at 7 out-patient visits (Days 1[Baseline], Weeks 4, 8, 12, 16, 20, 24).

Condition	Intervention	Phase
Osteoarthritis of the Knee	Drug: FX006 Drug: Normal Saline Drug: TCA IR	Phase 3

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Double-Blind, Randomized, Single-Dose Study to Assess the Safety and Efficacy of **FX006** for the Treatment of Pain in Patients With **Osteoarthritis** of the Knee

Resource links provided by NLM:

MedlinePlus related topics: Osteoarthritis

U.S. FDA Resources

Further study details as provided by Flexion Therapeutics, Inc.:

Primary Outcome Measures:

- Change from Baseline to Week 12 in the weekly mean of the average daily (24-hr) pain intensity score for **FX006** relative to placebo [Time Frame: 12 Weeks] [Designated as safety issue: No]

Secondary Outcome Measures:

- Change from Baseline to Week 8 in the weekly mean of the average daily (24-hr) pain intensity score for **FX006** relative to TCA IR [Time Frame: 8 Weeks] [Designated as safety issue: No]
- WOMAC C (function): change from Baseline to Week 12 for **FX006** relative to placebo [Time Frame: 12 Weeks] [Designated as safety issue: No]
- Patients' Global Impression of Change (PGIC) scale at Week 12 for **FX006** relative to placebo [Time Frame: 12 Weeks] [Designated as safety issue: No]
- Proportion of patients experiencing a >20% decrease in pain from baseline in weekly mean of the average daily (24-hr) pain intensity scores at Week 12 for **FX006** relative to placebo [Time Frame: 12 Weeks] [Designated as safety issue: No]
- Change from Baseline to Week 12 in the weekly mean of the average daily (24-hr) pain intensity scores for **FX006** relative to TCA IR

Estimated Enrollment:450

Study Start Date:February 2015

Estimated Study Completion Date:June 2016

Estimated Primary Completion Date:June 2016 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: FX006 40mg	Drug: FX006 Single intra-articular injection
Placebo Comparator: Normal Saline	Drug: Normal Saline Single intra-articular injection
Active Comparator: TCA IR 40mg	Drug: TCA IR Single intra-articular injection

► Eligibility

Ages Eligible for Study:40 Years and older

Genders Eligible for Study:Both

Accepts Healthy Volunteers:No

Criteria

Inclusion Criteria:

- Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
- Male or female >=40 years of age
- Has symptoms associated with OA of the index knee for at least 6 months prior to Screening
- Currently meets American College of Rheumatology (ACR) Criteria (clinical and radiological) for OA
- Kellgren-Lawrence (K-L) Grade 2 or 3 in the index knee per Screening X-ray
- Index knee pain for > 15 days over the last month
- Qualifying mean score on the 24-h average pain score (0-10 numeric rating scale)
- Body mass index (BMI) ≤ 40 kg/m2
- Willingness to abstain from use of restricted medications

Exclusion Criteria:

- Any condition that could possibly confound the patient's assessment of index knee pain in judgement of the investigator (i.e., ipsilateral hip OA, gout, radicular low back pain and hip pain that is referred to the knee that could cause misclassification, pain in any other area of the lower extremities or back that is equal or greater than the index knee pain)
- Fibromyalgia, Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease
- History of infection in the index knee
- Clinical signs and symptoms of active knee infection or crystal disease of the index knee within 1 month of Screening
- Unstable joint within 12 months of screening
- IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening
- IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
- Intramuscular (IM) or oral corticosteroids (investigational or marketed) within 1 month of Screening
- Any other IA investigational drug/biologic within 6 months of Screening
- Prior use of FX006
- Women of child-bearing potential not using effective contraception or who are pregnant or nursing

► Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT02357459

Contacts

Contact: Laura McKellar781-305-7777lmckellar@flexiontherapeutics.com

Contact: Amy Gauger781-305-7777agauger@flexiontherapeutics.com

Locations

United States, Arizona

Recruiting

Phoenix, Arizona, United States, 85023

Contact602-773-3030

Recruiting

Tucson, Arizona, United States, 85712
Contact 520-784-6140

United States, California

Recruiting

Anaheim, California, United States, 92801
Contact 714-780-0076

Recruiting

Canoga Park, California, United States, 91303
Contact 818-999-4673

Recruiting

San Diego, California, United States, 92103
Contact 858-278-3647

United States, Colorado

Recruiting

Denver, Colorado, United States, 80209
Contact 720-941-9363

United States, Florida

Recruiting

Atlantis, Florida, United States, 33462
Contact 561-968-2933

Recruiting

DeLand, Florida, United States, 32720
Contact 386-734-3710

Recruiting

Hialeah, Florida, United States, 33012
Contact 786-343-3902

Recruiting

Sarasota, Florida, United States, 34232
Contact 9415527875

Recruiting

West Palm Beach, Florida, United States, 33409
Contact 561-689-0606

United States, Kansas

Recruiting

Prairie Village, Kansas, United States, 66206
Contact 913-381-7180

United States, New Mexico

Recruiting

Albuquerque, New Mexico, United States, 87102
Contact 505-224-7407

United States, North Carolina

Recruiting

Charlotte, North Carolina, United States, 28209
Contact 704-527-6672

United States, Pennsylvania

Recruiting

Duncansville, Pennsylvania, United States, 16635
Contact 814-693-0030

United States, Tennessee

Recruiting

Knoxville, Tennessee, United States, 37912
Contact 865-244-4276

Sponsors and Collaborators

Flexion Therapeutics, Inc.

More Information

No publications provided

Responsible Party:	Flexion Therapeutics, Inc.
ClinicalTrials.gov Identifier:	NCT02357459 History of Changes
Other Study ID Numbers:	FX006-2014-008
Study First Received:	February 3, 2015
Last Updated:	April 10, 2015
Health Authority:	United States: Food and Drug Administration New Zealand: Ministry of Health Australia: Human Research Ethics Committee Hong Kong: Department of Health

Denmark: Danish Health and Medicines Authority
Estonia: The State Agency of Medicine
Lithuania: State Medicine Control Agency - Ministry of Health
Romania: National Medicines Agency

Keywords provided by Flexion Therapeutics, Inc.:

Osteoarthritis	Steroid
Knee	Intra-articular
Pain	Injection

Additional relevant MeSH terms:

Osteoarthritis	Joint Diseases
Osteoarthritis , Knee	Musculoskeletal Diseases
Arthritis	Rheumatic Diseases

ClinicalTrials.gov processed this record on May 03, 2015

Trial record 2 of 5 for: fx006 and osteoarthritis

Previous Study | Return to List | Next Study

Study of FX006 in Patients With Osteoarthritis of the Knee

This study has been completed.

Sponsor:
Flexion Therapeutics, Inc.

Information provided by (Responsible Party):
Flexion Therapeutics, Inc.

ClinicalTrials.gov Identifier:
NCT01487161

First received: December 5, 2011
Last updated: March 16, 2015
Last verified: March 2015
History of Changes

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

Purpose

The purpose of the study is to evaluate the safety, efficacy and pharmacokinetics of **FX006** in patients with **osteoarthritis** of the knee.

Condition	Intervention	Phase
Osteoarthritis of the Knee	Drug: FX006 Drug: Commercially available triamcinolone acetonide	Phase 2

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Safety/Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Double-Blind, Randomized, Parallel Group, Dose-Ranging Study Comparing **FX006** to Commercially Available Triamcinolone Acetonide Injectable Suspension in Patients With **Osteoarthritis** of the Knee

Resource links provided by NLM:

MedlinePlus related topics: [Osteoarthritis](#)

Drug Information available for: [Triamcinolone diacetate](#) [Triamcinolone acetonide](#) [Triamcinolone](#) [Triamcinolone hexacetonide](#)

[U.S. FDA Resources](#)

Further study details as provided by Flexion Therapeutics, Inc.:

- Primary Outcome Measures:
- Change from Baseline to each of Weeks 8, 10 and 12 in weekly mean of the average daily (24-hour) pain intensity score. [Time Frame: at 8, 10 and 12 weeks] [Designated as safety issue: No]
 - Incidence of treatment emergent adverse events [Time Frame: through 12 weeks] [Designated as safety issue: Yes]
- Secondary Outcome Measures:
- Change from Baseline to each of Weeks 1, 2, 3, 4, 5, 6, 7, 9 and 11 in weekly mean of the average (24-hour) pain intensity score. [Time Frame: weekly through 12 weeks] [Designated as safety issue: No]
 - Time of onset of pain relief [Time Frame: weekly through 12 weeks] [Designated as safety issue: No]
 - Continuous responder at each study week [Time Frame: weekly through 12 weeks] [Designated as safety issue: No]
 - WOMAC A (pain subscale) change from Baseline [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]
 - WOMAC B (stiffness subscale) change from Baseline [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]
 - WOMAC C (function subscale) change from Baseline [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]
 - WOMAC (total) change from Baseline [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]
 - Percent of responders (defined as patients with high improvement in pain or function) according to OMERACT-OARSI criteria [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]
 - Change in patient's and clinical observer's global impression of change scores [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]
 - Average weekly and total consumption of rescue medications [Time Frame: weekly through 12 weeks] [Designated as safety issue: No]
 - Pharmacokinetic profile [Time Frame: through 12 weeks] [Designated as safety issue: No]
 - WOMAC A1 (pain on walking question) change from Baseline [Time Frame: at 1, 2, 4, 8 and 12 weeks] [Designated as safety issue: No]

Enrollment: 229
Study Start Date: June 2012
Study Completion Date: May 2013
Primary Completion Date: May 2013 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: FX006 10 mg	Drug: FX006 Single intra-articular injection
Experimental: FX006 40 mg	Drug: FX006 Single intra-articular injection
Experimental: FX006 60 mg	Drug: FX006 Single intra-articular injection
Active Comparator: commercially available triamcinolone acetonide (40 mg)	Drug: Commercially available triamcinolone acetonide Single intra-articular injection

Detailed Description:
This study will be a multi-center, randomized, double-blind, active comparator, parallel-group, single dose design.
Up to 224 patients with knee OA will be randomized to be treated with a single IA injection of either 10, 40, or 60 mg of FX006 or 40 mg of Kenalog-40.
Each patient will be evaluated for a total of 12 weeks following a single IA injection. Following screening, safety and efficacy and PK will be evaluated at 7 out-patient visits (Days 1 [Baseline], 2, 8, 15, 29, 57 and 85).
Analgesic effect will be assessed using weekly average of daily (24 hour) pain intensity score, Western Ontario & McMaster University Osteoarthritis Index (WOMAC) and patient and clinical global impression of change.

► Eligibility

Ages Eligible for Study: 40 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria
Main Inclusion Criteria:

- Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
- Male or female >=40 years of age
- Diagnosis of unilateral or bilateral OA of the knee for at least 6 months prior to Screening with confirmation of OA according to American College of Rheumatology Criteria for Classification of Idiopathic OA of the Knee (clinical and radiological) based on an X-ray performed within 6 months prior to Screening or during the Screening period
- Qualifying mean score on the 24-h average pain score (0-10 numeric rating scale)
- Body mass index (BMI) ≤ 40 kg/m2
- Willingness to abstain from use of restricted medications

Main Exclusion Criteria

- Ipsilateral hip OA
- Fibromyalgia, chronic pain syndrome or other concurrent medical or arthritic conditions which could interfere with the evaluation of the index knee
- History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis or amyloidosis
- History of arthritides due to crystals (e.g., gout, pseudogout)
- History of infection in the index joint
- Clinical signs and symptoms of active knee infection or crystal disease of the index knee
- Presence of surgical hardware or other foreign body in the index knee
- Unstable joint (such as a torn anterior cruciate ligament)
- IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening
- IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
- Oral, inhaled and intranasal corticosteroids (investigational or marketed) within 1 month of Screening
- Prior arthroscopic or open surgery of the index knee within 12 months of Screening
- Planned/anticipated surgery of the index knee during the study period
- Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ
- Insulin-dependent diabetes
- Active psychiatric disorder including psychosis and major depressive disorder
- History of or active Cushing's syndrome
- Any other clinically significant acute or chronic medical conditions (e.g., uncontrolled diabetes)
- Skin breakdown at the knee where the injection would take place
- Women of child-bearing potential not using effective contraception or who are pregnant or nursing

► **Contacts and Locations**

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT01487161

Locations

- United States, Arizona**
Tucson, Arizona, United States
- United States, Pennsylvania**
Duncansville, Pennsylvania, United States
- Australia, New South Wales**
Broadmeadow, New South Wales, Australia
Kogarah, New South Wales, Australia
St. Leonards, New South Wales, Australia
Wollongong, New South Wales, Australia
- Australia, Queensland**
Kippa-Ring, Queensland, Australia
Maroochyndore, Queensland, Australia
Sherwood, Queensland, Australia
- Australia, Victoria**
Clayton, Victoria, Australia
Malvern East, Victoria, Australia

- Canada, Nova Scotia**
Halifax, Nova Scotia, Canada
- Canada, Ontario**
Etobicoke, Ontario, Canada
Newmarket, Ontario, Canada
Sarnia, Ontario, Canada
St. Catherine's, Ontario, Canada
Thornhill, Ontario, Canada
Waterloo, Ontario, Canada
Windsor, Ontario, Canada

- Canada, Quebec**
Montreal, Quebec, Canada
Sainte-Foy, Quebec, Canada

Sponsors and Collaborators

Flexion Therapeutics, Inc.

Investigators

Study Director: Neil Bodick, MD, PhD Flexion Therapeutics

► **More Information**

No publications provided

Responsible Party:

ClinicalTrials.gov Identifier:

Other Study ID Numbers:

Study First Received:

Last Updated:

Health Authority:

Flexion Therapeutics, Inc.

NCT01487161 [History of Changes](#)

FX006-2011-001

December 5, 2011

March 16, 2015

Canada: Health Canada
Australia: Therapeutics Goods Administration (TGA)
United States: Food and Drug Administration

Keywords provided by Flexion Therapeutics, Inc.:

Osteoarthritis	steroid
Knee	intra-articular
pain	injection

Additional relevant MeSH terms:

Osteoarthritis	Enzyme Inhibitors
Osteoarthritis, Knee	Glucocorticoids
Arthritis	Hormones
Joint Diseases	Hormones, Hormone Substitutes, and Hormone Antagonists
Musculoskeletal Diseases	Immunologic Factors
Rheumatic Diseases	Immunosuppressive Agents
Triamcinolone	Molecular Mechanisms of Pharmacological Action
Triamcinolone Acetonide	Pharmacologic Actions
Triamcinolone diacetate	Physiological Effects of Drugs

Triamcinolone hexacetonide
Anti-Inflammatory Agents

Therapeutic Uses

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ClinicalTrials.gov processed this record on May 03, 2015

Trial record 3 of 5 for: fx006 and osteoarthritis

Previous Study | Return to List | Next Study

Study of FX006 vs Normal Saline in Patients With Osteoarthritis of the Knee

This study is ongoing, but not recruiting participants.

Sponsor:
Flexion Therapeutics, Inc.

Information provided by (Responsible Party):
Flexion Therapeutics, Inc.

ClinicalTrials.gov Identifier:
NCT02116972

First received: April 15, 2014
Last updated: February 24, 2015
Last verified: February 2015
History of Changes

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

Purpose

This study is a double-blind, randomized, parallel group, dose-ranging, single dose design. The study will be conducted in male and female patients ≥ 40 years of age with **osteoarthritis** (OA) of the knee.

Approximately 300 patients with OA of the knee will be randomized to one of three treatment groups (1:1:1) and treated with a single intra-articular (IA) injection of:

- 20 mg **FX006**,
- 40 mg **FX006**, or
- normal saline.

Each patient will be evaluated for a total of 24 weeks following a single IA injection. Following screening, safety and efficacy will be evaluated at 6 out-patient visits (Days 1 [Baseline], Weeks 4, 8, 12, 16, 20 and 24).

Condition	Intervention	Phase
Osteoarthritis of the Knee	Drug: FX006 Drug: Normal saline	Phase 2

Study Type: Interventional

Study Design: Allocation: Randomized
Endpoint Classification: Efficacy Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Double-Blind, Randomized, Parallel Group, Dose-Ranging Study to Assess the Safety and Efficacy of **FX006** for the Treatment of Pain in Patients With **Osteoarthritis** of the Knee

Resource links provided by NLM:

MedlinePlus related topics: [Osteoarthritis](#)

[U.S. FDA Resources](#)

Further study details as provided by Flexion Therapeutics, Inc.:

Primary Outcome Measures:

- Change from Baseline to Weekly 12 in the weekly mean of the average daily (24-hour) pain intensity score. [Time Frame: 12 weeks]
[Designated as safety issue: No]

Secondary Outcome Measures:

- WOMAC C (function): change from Baseline to Week 12 [Time Frame: Week 12] [Designated as safety issue: No]
- Patient Global Impression of Change (PGIC) at Week 12 [Time Frame: Week 12] [Designated as safety issue: No]
- WOMAC A (pain): change from Baseline to Week 12 [Time Frame: Week 12] [Designated as safety issue: No]
- Proportion of patients experiencing a >20% decrease in pain from baseline in weekly mean of the average daily (24-hr) pain intensity scores at Week 12 [Time Frame: Week 12] [Designated as safety issue: No]
- Incidence of treatment emergent adverse events [Time Frame: Through Week 24] [Designated as safety issue: Yes]

Estimated Enrollment: 300

Study Start Date: April 2014

Estimated Study Completion Date: December 2015

Estimated Primary Completion Date: December 2015 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: FX006 20 mg	Drug: FX006 Single intra-articular injection
Experimental: FX006 40 mg	Drug: FX006 Single intra-articular injection
Placebo Comparator: Normal saline	Drug: Normal saline Single intra-articular injection

► Eligibility

Ages Eligible for Study: 40 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Main Inclusion Criteria:

- Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
- Male or female >=40 years of age
- Has documented diagnosis of OA of the index knee made at least 6 months prior to Screening
- Currently meets American College of Rheumatology (ACR) Criteria (clinical and radiological) for OA
- Kellgren-Lawrence (K-L) Grade 2 or 3 in the index knee per Screening X-ray
- Qualifying mean score on the 24-h average pain score (0-10 numeric rating scale)
- Body mass index (BMI) ≤ 40 kg/m2
- Willingness to abstain from use of restricted medications

Main Exclusion Criteria:

- Ipsilateral hip OA
- Fibromyalgia, chronic pain syndrome or other concurrent medical or arthritic conditions which could interfere with the evaluation of the index knee
- History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis or amyloidosis
- History of arthritides due to crystals (e.g., gout, pseudogout)
- History or clinical signs and symptoms of infection in the index joint
- Knee pain that is not clinically attributable to OA of the knee (e.g., radicular low back pain and hip pain that is referred to the knee that could cause misclassification)
- Pain in any other area of the lower extremities or back that is equal to or greater than the index knee pain
- IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening
- IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
- Intramuscular (IM) corticosteroids (investigational or marketed) within 3 months of Screening
- Oral corticosteroids (investigational or marketed) within 1 month of Screening
- Inhaled, intranasal and topical corticosteroids (investigational or marketed) within 2 weeks of Screening
- Any other IA investigational drug/biologic within 6 months of Screening
- Prior use of FX006
- Women of child-bearing potential not using effective contraception or who are pregnant or nursing

► Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT02116972

 Show 44 Study Locations

Sponsors and Collaborators

Flexion Therapeutics, Inc.

► More Information

No publications provided

Responsible Party: Flexion Therapeutics, Inc.
ClinicalTrials.gov Identifier: [NCT02116972](#) [History of Changes](#)
Other Study ID Numbers: **FX006-2014-006**
Study First Received: April 15, 2014
Last Updated: February 24, 2015
Health Authority: United States: Food and Drug Administration

107 105

Keywords provided by Flexion Therapeutics, Inc.:

Osteoarthritis	steroid
Knee	intra-articular
pain	injection

Additional relevant MeSH terms:

Osteoarthritis	Joint Diseases
Osteoarthritis, Knee	Musculoskeletal Diseases
Arthritis	Rheumatic Diseases

ClinicalTrials.gov processed this record on May 03, 2015

Trial record 4 of 5 for: fx006 and osteoarthritis

Previous Study | Return to List | Next Study

Pharmacokinetic and Pharmacodynamic Study of FX006 in Patients With Osteoarthritis of the Knee

This study has been completed.

Sponsor:
Flexion Therapeutics, Inc.

Information provided by (Responsible Party):
Flexion Therapeutics, Inc.

ClinicalTrials.gov Identifier:
NCT01487200

First received: December 5, 2011
Last updated: November 16, 2012
Last verified: November 2012
History of Changes

Full Text View

Tabular View

No Study Results Posted

Disclaimer

How to Read a Study Record

Purpose

The purpose of this study is to evaluate the safety, pharmacokinetics and pharmacodynamics of **FX006** in patients with **osteoarthritis** of the knee.

Condition	Intervention	Phase
Osteoarthritis of the Knee	Drug: FX006 Drug: commercially available triamcinolone acetonide	Phase 2

Study Type: Interventional
Study Design: Allocation: Randomized
Endpoint Classification: Pharmacokinetics/Dynamics Study
Intervention Model: Parallel Assignment
Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
Primary Purpose: Treatment

Official Title: A Double-Blind, Randomized, Parallel Group, Active Comparator Study to Evaluate the Safety, Pharmacokinetics, and Pharmacodynamic Effects (HPA Axis) of **FX006** in Patients With **Osteoarthritis** of the Knee

Resource links provided by NLM:

MedlinePlus related topics: [Osteoarthritis](#)

Drug Information available for: [Triamcinolone diacetate](#) [Triamcinolone acetonide](#) [Triamcinolone](#) [Triamcinolone hexacetonide](#)

[U.S. FDA Resources](#)

Further study details as provided by Flexion Therapeutics, Inc.:

- Primary Outcome Measures:
- Change from baseline in 24-hour weighted mean serum cortisol [Time Frame: at Day 1-2, Day 14-15 (Week 2) and Day 42-43 (Week 6)] [Designated as safety issue: No]
 - Incidence of treatment emergent adverse events [Time Frame: through 6 weeks] [Designated as safety issue: Yes]
 - Characterize the pharmacokinetic profile [Time Frame: Day 1 (pre-dose and at 1, 2, 4, 6, 8, 12 and 24 hours post dose) and Days 3, 4, 5, 8, 15, 22, 29, 36 and 43] [Designated as safety issue: No]
- Secondary Outcome Measures:
- Change from baseline in 24-hour urinary free cortisol excretion [Time Frame: at Day 1-2, Day 14-15 (Week 2) and Day 42-43 (Week 6)] [Designated as safety issue: No]
 - Total 24-hour urinary free cortisol excretion [Time Frame: at Day 1-2, Day 14-15 (Week 2) and Day 42-43 (Week 6)] [Designated as safety issue: No]
 - Change from baseline to each measured time point post-dose in morning serum cortisol [Time Frame: through Week 6] [Designated as safety issue: No]

Enrollment: 24
Study Start Date: July 2012
Study Completion Date: November 2012
Primary Completion Date: November 2012 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
------	------------------------

Experimental: FX006 10mg	Drug: FX006 single intra-articular injection
Experimental: FX006 40mg	Drug: FX006 single intra-articular injection
Experimental: FX006 60 mg	Drug: FX006 single intra-articular injection
Active Comparator: commercially available triamcinolone acetonide (40 mg)	Drug: commercially available triamcinolone acetonide single intra-articular injection

Detailed Description:
This study will be a double-blind, randomized, parallel-group, active comparator design.
Twenty-four patients with knee osteoarthritis (OA) will be randomized to be treated with a single IA injection of 10, 40, or 60 mg of FX006 or 40 mg of commercially available triamcinolone acetonide.
Each patient will be evaluated for a total of 6 weeks following a single IA injection. Following screening, safety, PK and pharmacodynamics will be evaluated during one (1) 48-hour in-patient period (Day -1 to Day 2), two (2) 24-hour in-patient periods (Day 14-15 and Day 42-43) and seven (7) out-patient visits (Days 3, 4, 5, 8, 22, 29 and 36).

► Eligibility

Ages Eligible for Study: 35 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Main Inclusion Criteria:

- Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
- Male or female >=35 years of age
- Diagnosis of unilateral or bilateral OA of the knee for at least 6 months prior to Screening with confirmation of OA according to American College of Rheumatology Criteria for Classification of Idiopathic OA of the Knee (clinical and radiological) based on an X-ray performed within 6 months prior to Screening or during the Screening period
- Body mass index (BMI) ≤ 40 kg/m2
- Willingness to abstain from use of the protocol-specified restricted medications

Main Exclusion Criteria:

- History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis or amyloidosis
- History of arthritides due to crystals (e.g., gout, pseudogout)
- History of infection in the index joint
- Clinical signs and symptoms of active knee infection or crystal disease of the index knee
- Presence of surgical hardware or other foreign body in the index knee
- Unstable joint (such as a torn anterior cruciate ligament)
- IA corticosteroid (investigational or marketed) in any joint within 3 months of Screening
- IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
- Oral, inhaled or intranasal corticosteroids (investigational or marketed) within 1 month of Screening
- Prior arthroscopic or open surgery of the index knee within 12 months of Screening
- Planned/anticipated surgery of the index knee during the study period
- History of or active malignancy, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ within 5 years
- Insulin-dependent diabetes
- History of or active Cushing's syndrome
- Any other clinically significant acute or chronic medical conditions (e.g., uncontrolled diabetes)
- Skin breakdown at the knee where the injection would take place
- Women of child-bearing potential not using effective contraception or who are pregnant or nursing

► Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT01487200

Locations

- Australia, South Australia**
Adelaide, South Australia, Australia
- Australia, Western Australia**
Perth, Western Australia, Australia

Sponsors and Collaborators

Flexion Therapeutics, Inc.

More Information

No publications provided

Responsible Party: Flexion Therapeutics, Inc.
ClinicalTrials.gov Identifier: [NCT01487200](#) [History of Changes](#)
Other Study ID Numbers: **FX006-2011-002**
Study First Received: December 5, 2011
Last Updated: November 16, 2012
Health Authority: Australia: Therapeutics Goods Administraion (TGA)

Keywords provided by Flexion Therapeutics, Inc.:

Osteoarthritis
Knee
Steroid
intra-articular
injection

Additional relevant MeSH terms:

Osteoarthritis	Enzyme Inhibitors
Osteoarthritis, Knee	Glucocorticoids
Arthritis	Hormones
Joint Diseases	Hormones, Hormone Substitutes, and Hormone Antagonists
Musculoskeletal Diseases	Immunologic Factors
Rheumatic Diseases	Immunosuppressive Agents
Triamcinolone	Molecular Mechanisms of Pharmacological Action
Triamcinolone Acetonide	Pharmacologic Actions
Triamcinolone diacetate	Physiological Effects of Drugs
Triamcinolone hexacetonide	Therapeutic Uses
Anti-Inflammatory Agents	

ClinicalTrials.gov processed this record on May 03, 2015

Trial record 5 of 5 for: fx006 and osteoarthritis
Previous Study | Return to List | Next Study

Study to Characterize the Local Duration of Exposure From FX006 in Patients With Osteoarthritis of the Knee

This study has been completed.

Sponsor:
Flexion Therapeutics, Inc.

Information provided by (Responsible Party):
Flexion Therapeutics, Inc.

ClinicalTrials.gov Identifier:
NCT02003365

First received: November 18, 2013
Last updated: November 3, 2014
Last verified: November 2014
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

Purpose

This study will be an open-label, single administration design, conducted in patients with OA of the knee. Patients will be enrolled sequentially with 8 to 10 patients per Cohort as follows:
Cohort A: FX006 40 mg, Final Visit at Week 20 Cohort B: FX006 40 mg, Final Visit at Week 16 Cohort C: FX006 10 mg, Final Visit at Week 12 Cohort D: FX006 40 mg, Final Visit at Week 12 Cohort E: Triamcinolone acetonide immediate-release (TCA IR) 40 mg, Final Visit Week 12
Each patient will be evaluated for up to 12, 16 or 20 weeks following a single intra-articular (IA) injection of FX006 at 10 mg or 40 mg or TCA IR 40 mg, depending on the assigned Cohort. Following the screening visit, safety will be evaluated at three (3) out-patient visits and synovial fluid will be collected at Day 1 for baseline measurements and the Final Visit for drug concentration measurements.

Condition	Intervention	Phase
Osteoarthritis of the Knee	Drug: FX006 10 mg Drug: FX006 40 mg Drug: TCA IR 40 mg	Phase 2

Study Type: Interventional
Study Design: Allocation: Non-Randomized
Endpoint Classification: Pharmacokinetics Study
Intervention Model: Single Group Assignment
Masking: Open Label
Primary Purpose: Treatment

Official Title: An Open-label, Single Administration Study to Characterize the Local Duration of Exposure of Triamcinolone Acetonide From FX006 in Patients With Osteoarthritis (OA) of the Knee

Resource links provided by NLM:

MedlinePlus related topics: Osteoarthritis
Drug Information available for: Triamcinolone diacetate Triamcinolone acetonide Triamcinolone Triamcinolone hexacetonide
U.S. FDA Resources

Further study details as provided by Flexion Therapeutics, Inc.:

Primary Outcome Measures:
• Measure the concentration of triamcinolone acetoneide in synovial fluid [Time Frame: 12 to 20 weeks] [Designated as safety issue: No]

Secondary Outcome Measures:
• Incidence of treatment emergent adverse events [Time Frame: 12 to 20 weeks] [Designated as safety issue: Yes]

Enrollment: 50
Study Start Date: November 2013
Study Completion Date: June 2014
Primary Completion Date: May 2014 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
Experimental: FX006 10 mg FX006 10 mg, single IA injection	Drug: FX006 10 mg

Experimental: FX006 40 mg FX006 40 mg single IA injection	Drug: FX006 40 mg
Active Comparator: TCA IR TCA IR 40 mg single IA injection	Drug: TCA IR 40 mg

► Eligibility

Ages Eligible for Study: 40 Years and older
Genders Eligible for Study: Both
Accepts Healthy Volunteers: No

Criteria

Key Inclusion Criteria:

- Written consent to participate in the study
- Willingness and ability to comply with the study procedures and visit schedules and ability to follow verbal and written instructions
- Has documented diagnosis of OA of the index knee made at least 6 months prior to Screening
- Currently meets American Collage of Rheumatology Criteria (clinical and radiological) for OA
- Index knee pain for >15 days over the last month
- Body mass index (BMI) ≤ 40 kg/m2
- Ambulatory and in good general health

Key Exclusion Criteria:

- History of Reiter's syndrome, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, arthritis associated with inflammatory bowel disease, sarcoidosis or amyloidosis
- History of arthritides due to crystals (e.g., gout, pseudogout)
- History of infection in the index joint
- Clinical signs and symptoms of active knee infection or crystal disease of the index knee
- Presence of surgical hardware or other foreign body in the index knee
- Unstable joint (such as a torn anterior cruciate ligament) within 12 months of Screening
- IA corticosteroid (investigational or marketed) in any joint within 6 months of Screening
- IA hyaluronic acid (investigational or marketed) in the index knee within 6 months of Screening
- Oral corticosteroids (investigational or marketed) within 1 month of Screening
- Inhaled, intranasal and topical corticosteroids (investigational or marketed) within 2 weeks of Screening
- Any other IA investigational drug/biologic within 6 months of Screening
- Prior use of FX006
- Prior arthroscopic or open surgery of the index knee within 12 months of Screening
- Planned/anticipated surgery of the index knee during the study period
- Active or history of malignancy within the last 5 years, with the exception of resected basal cell carcinoma, squamous cell carcinoma of the skin, or resected cervical atypia or carcinoma in situ

► Contacts and Locations

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see [Learn About Clinical Studies](#).

Please refer to this study by its ClinicalTrials.gov identifier: NCT02003365

Locations

- United States, Kentucky
Paducah, Kentucky, United States
- United States, Pennsylvania
Ducansville, Pennsylvania, United States
- United States, Texas
Dallas, Texas, United States

Sponsors and Collaborators

Flexion Therapeutics, Inc.

► More Information

No publications provided

Responsible Party: Flexion Therapeutics, Inc.
ClinicalTrials.gov Identifier: NCT02003365 [History of Changes](#)
Other Study ID Numbers: FX006-2013-005
Study First Received: November 18, 2013
Last Updated: November 3, 2014

Health Authority: United States: Food and Drug Administration

Keywords provided by Flexion Therapeutics, Inc.:

osteoarthritis
knee
steroids

FX006
triamcinolone acetonide
synovial fluid

Additional relevant MeSH terms:

Osteoarthritis
Osteoarthritis, Knee
Arthritis
Joint Diseases
Musculoskeletal Diseases
Rheumatic Diseases
Triamcinolone
Triamcinolone Acetonide
Triamcinolone diacetate
Triamcinolone hexacetonide
Anti-Inflammatory Agents

Enzyme Inhibitors
Glucocorticoids
Hormones
Hormones, Hormone Substitutes, and Hormone Antagonists
Immunologic Factors
Immunosuppressive Agents
Molecular Mechanisms of Pharmacological Action
Pharmacologic Actions
Physiological Effects of Drugs
Therapeutic Uses

ClinicalTrials.gov processed this record on May 03, 2015

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
RECIBO DE CA	SIC ** RECIBO **	999999999	48911	29/04/2015	530.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	48917	29/04/2015	536.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	48918	29/04/2015	536.000.00
RECIBO DE CA	SIC ** RECIBO **	999999999	49154	30/04/2015	1.000.00

*** Conceptos Pagados ***

CANT. RENTISTICO	CONCEPTO	Vr.UNDITARIO	Vr.CONCEPTO
1 50005-01-03 CAMBIO DE MODALIDAD Y MODIFICACIONES	EN N. CREACION CORRECCION A SOLICITUD EN TRAMITE / MODIFICA	132.000.00	132.000.00
			\$132.000.00

SON: **CIENTO TREINTA Y DOS MIL PESOS MONEDA CORRIENTE***

Responsable: _____

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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