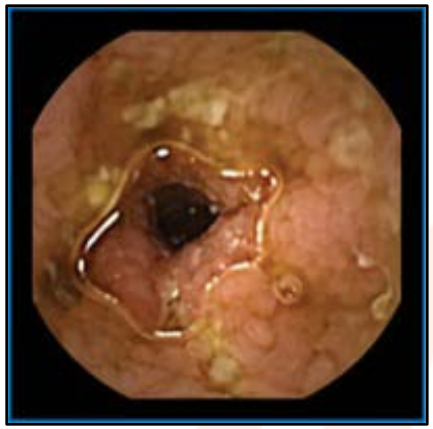
Oral Beclomethasone 17, 21-Dipropionate (BDP) in Pediatric Crohn's Disease

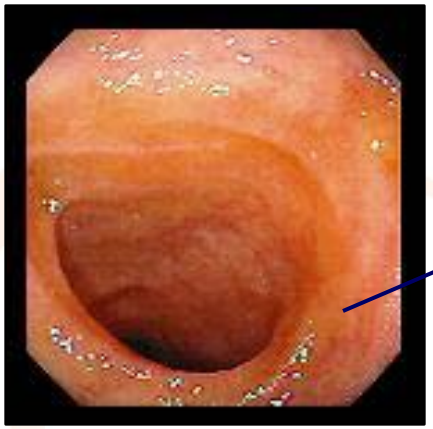
Non-Confidential Summary

January 15, 2018

SOLIGENIX

Pediatric Crohn's Disease – Disease Overview

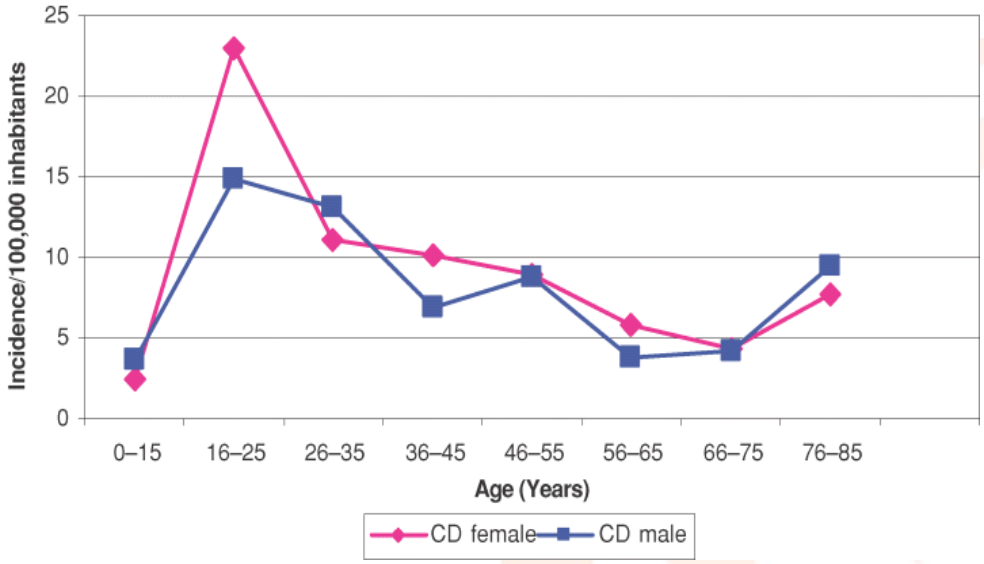


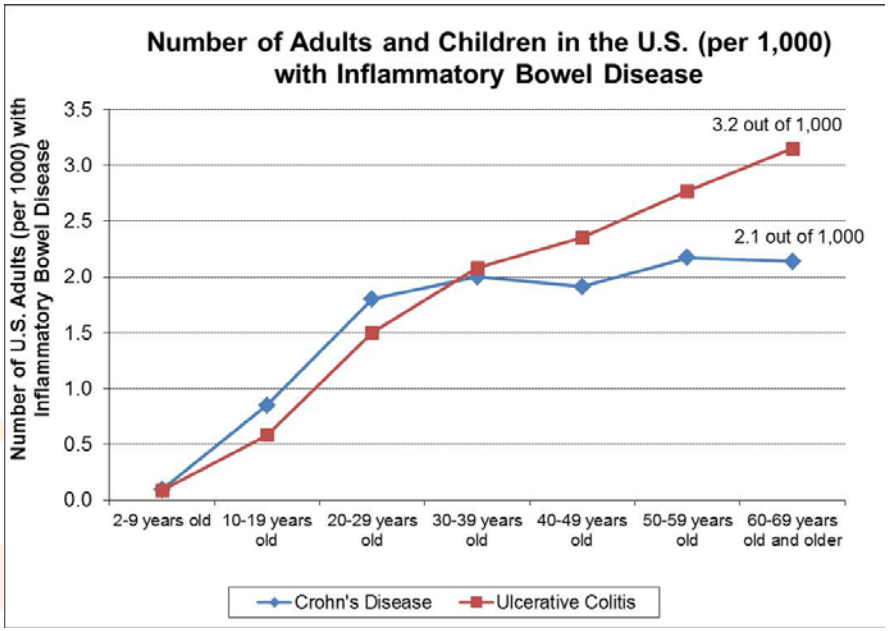


Normal mucosa under endoscopy

- **About pediatric Crohn's disease**
  - Chronic inflammatory disorder of the gastrointestinal (GI) tract
  - Diarrhea, rectal bleeding and abdominal pain
- **Resulting in growth failure, malnutrition, pubertal delay and bone demineralization**
- **Over 160,000 children/adolescents with Crohn's disease worldwide**
  - $200 million global market potential
- **Location of disease**
  - Adult is predominantly lower GI tract
  - 50% of children have involvement in the upper GI tract

Age Distribution of Crohn's Disease



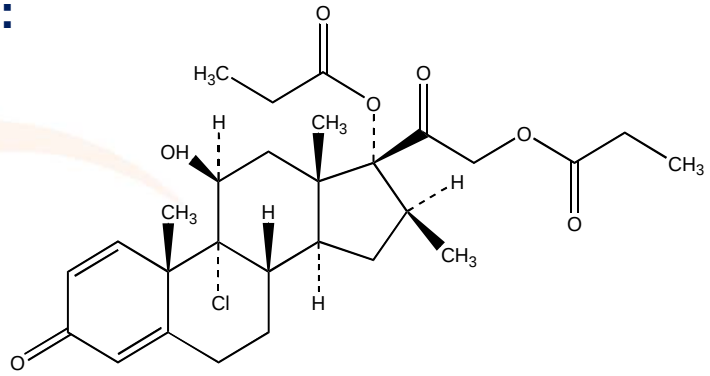


Treatment in Pediatric Crohn's Disease

- **No approved drug for *mild-to-moderate* pediatric Crohn's disease in the US; *unmet medical need***
- **Flare-ups are generally treated with systemic steroids (e.g., oral or IV prednisone)**
  - Associated with significant side-effects including hypertension, glucose intolerance, bone osteopenia, cataracts, decreased linear growth and increased risk of infections
  - Treatment is minimized to 2-4 weeks and then tapered over an 8-10 week period
  - Approximately 30% of CD patients become dependent on corticosteroid treatment and dose reduction results in clinical flares
- **Biologics (e.g., Humira®) approved as second line therapy due to their BLACK BOX warning for cancer and increased risk of infection**
- **Oral BDP treatment provides:**
  - Anti-inflammatory steroid activity localized to BOTH the upper and lower GI tract
  - Limited systemic steroid exposure (minimizing side effects)
  - Safety profile in children with multiple formulations of BDP well established, including specific safety/PK testing in adolescents

SGX203

- **Finished drug product (FDP) research name: SGX203**
- **Active pharmaceutical ingredient (API): beclomethasone 17,21-dipropionate (BDP)**
  - Well-characterized steroidal anti-inflammatory
    - Both the parent molecule BDP and the primary metabolite (BMP) are pharmacologically active
  - Used for over 35 years in other topical formulations:
    - Inhaled forms for asthma (Clenil®, Qvar®)
    - Nasal forms for rhinitis (Beconase®, Alanase®, Vancenase®)
    - Creams for inflammatory skin disorders (Propaderm®)



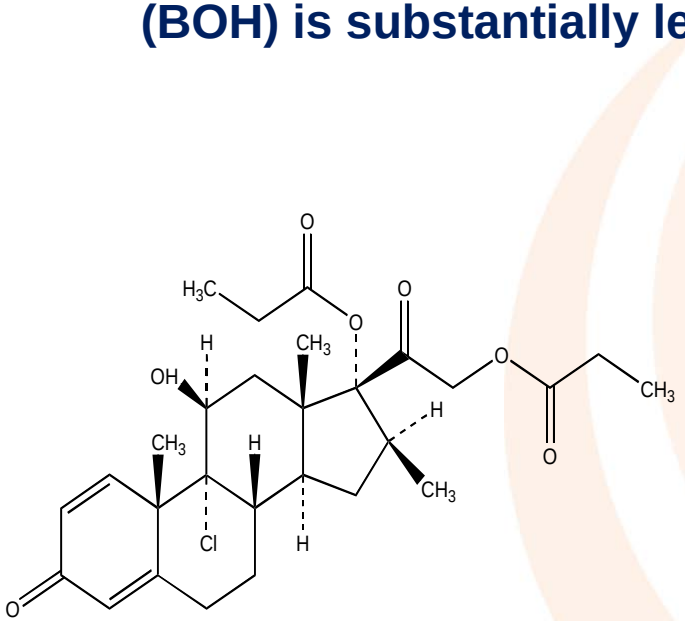
- **Proprietary two-tablet formulation with immediate release and delayed release (enteric coated) pills**
  - Provides coverage for BOTH the proximal and distal GI tract
  - “Topical steroid” for anti-inflammatory treatment of the GI tract minimizing deleterious systemic steroid exposure
  - Intellectual property for proprietary formulation expires 2022
  - Orphan drug designation provides 7 years US market exclusivity

Clinical & Regulatory Status

- **API and FDP cGMP manufacturing established**
  - Detailed preclinical studies demonstrate significant tissue exposure to BDP and its active metabolite while circulating concentrations remain low
- **FDA Orphan drug designation granted**
- **FDA Fast track status granted**
- **FDA agreement on Phase 3 clinical study design**
  - Protocol is cleared and “ready to go”
  - Drug product can be manufactured at will
  - Primarily enrolling in the US with some European countries/sites already identified
- **NDA will be 505(b)(2)**
- **Potential for NIH SBIR and FDA Orphan grant funding**

Metabolism of BDP

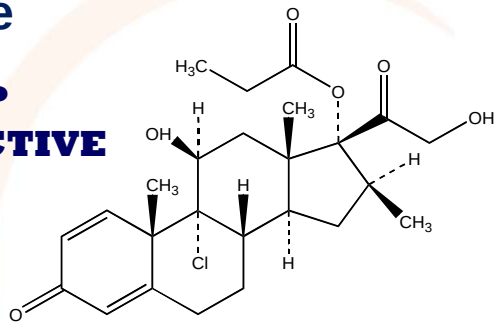
- **Beclomethasone 17,21-dipropionate (BDP) and its primary metabolite beclomethasone 17-monopropionate (BMP) are the most active in terms of steroidal activity while the secondary metabolite beclomethasone (BOH) is substantially less active**



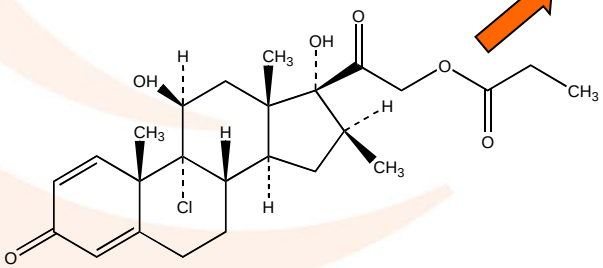
Beclomethasone 17,21-dipropionate (BDP)

BDP
ACTIVE

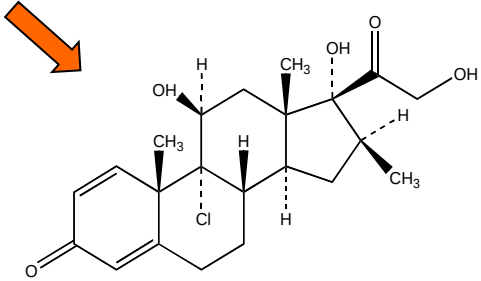
BMP
MORE ACTIVE



17-Beclomethasone monopropionate (17-BMP)



21-Beclomethasone monopropionate (21-BMP)



Beclomethasone (BOH)

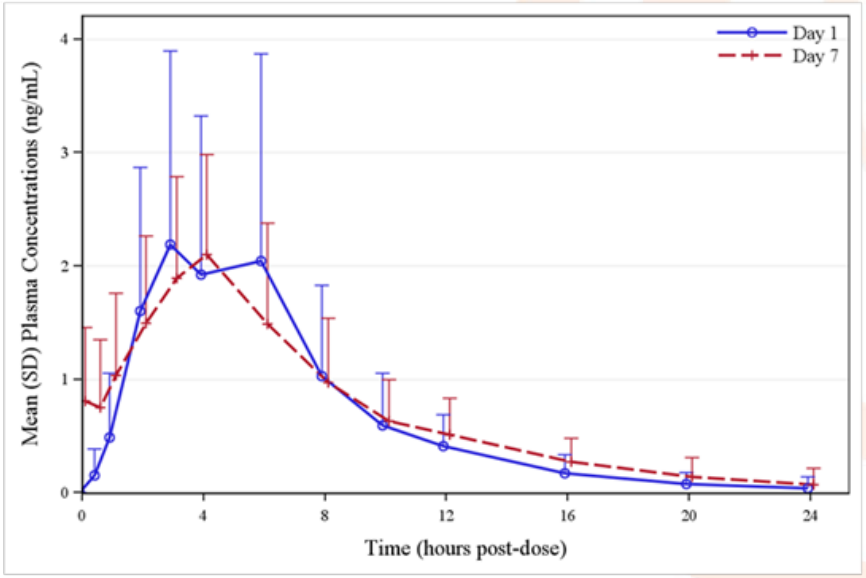
BOH
LESS ACTIVE

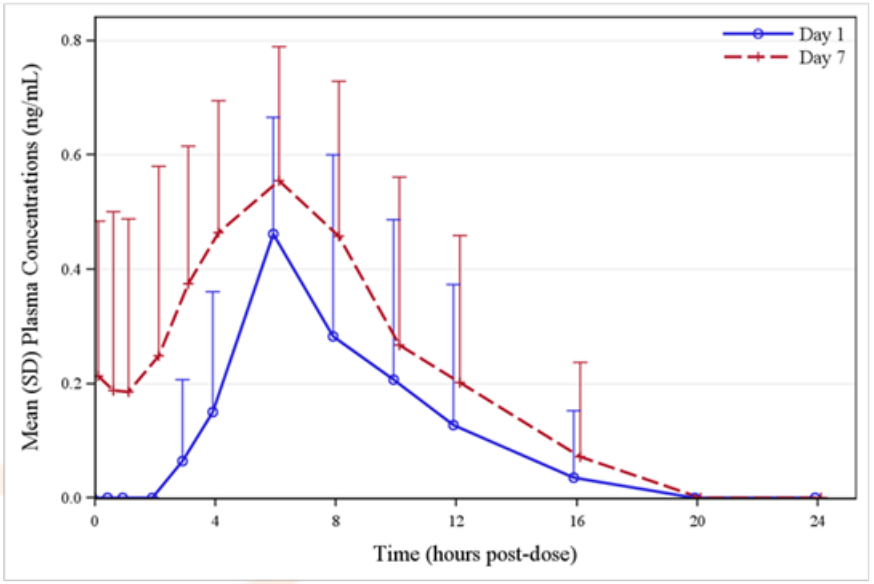
Phase 1 Study: BDP-PCD-01

- **Open-label, single-period, repeating dose study**
  - 24 healthy subjects (15 male, 9 female)
  - Ages 18 to 22 years of age (mean 20.3)
  - 13 (54.2%) were black and 11 (45.8 %) were white
  - BDP administered as 6 or 12 mg as a single oral dose
  - BDP administered as a 6 mg oral dose for 7 days
  - No change in PK after 7 days treatment compared to first day
- **Multiple doses of BDP were safe and well tolerated**
  - No significant adverse events reported
  - No effect upon bone metabolism

Phase 1 Study: PK Outcomes

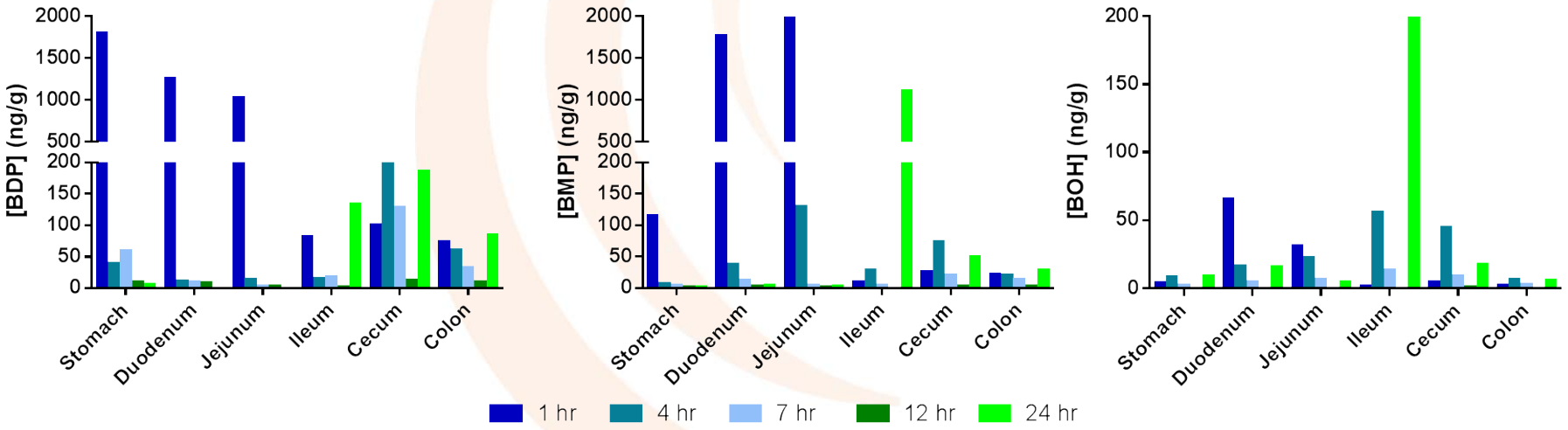
- **Pharmacokinetics Analysis:**
  - No BDP was detected in blood following BDP administration
  - BOH was only consistently measurable in 11 (50%)
  - 17-BMP metabolite levels were 3-fold higher than BOH





Nonclinical Tissue Profile

- **Study conducted in mini-pigs using the same dosing paradigm as human clinical study, with a daily dose of 8 mg/day**
- **BDP and BMP concentrations higher than BOH concentrations**
- ***Good coverage achieved throughout the GI tract***



Pivotal Study BDP-PCD-02: Design Items

- **Comparator choice**
  - Historic control unacceptable for pivotal Phase 2/3 study
  - Prednisone: standard of care but unapproved drug for pediatric Crohn's disease
  - Remicade®/Humira®: completely different mechanism of action with substantially different effects and timing of benefit
  - Placebo control: ethically unacceptable in this patient population
  - Demonstration of dose effect; high dose/low dose
- **Endpoint choice**
  - Biologics and most approved adult Crohn's drugs used improvement in disease activity indices (Pediatric Crohn's Disease Activity Index [PCDAI] or CDAI)
  - FDA recently changed their opinion on the utility of PCDAI and will not approve on improvement of standard indices
- **Final Phase 3 protocol design extensively negotiated with FDA**

Phase 3 Study: BDP-PCD-02

- **Pivotal adaptive design (bridging Phase 2 / 3 in a single study)**
- **Randomization 2:1:2**
- **Three Dose Regimens with 60 subjects each in the 1 mg and 12 mg dose group and 30 in the 6 mg dose group**
  - Initial 8 week treatment with primary analysis at end of Week 8
  - Each 8 week treatment is followed by a 4 week taper
- **Adaptive design allowing**
  - Independent Data Monitoring Committee (DMC)
  - At interim analysis after 90 patients
    - Halt for futility
    - Halt for overwhelming efficacy
    - Re-size based observed response rates compared to estimated rates
- **Primary Efficacy Endpoint**
  - To compare the rate of resolution of the Crohn's Disease signs and symptoms:
    - Abdominal pain and diarrhea; and
    - Normalization of serum albumin and hematocrit

Phase 3 Study: BDP-PCD-02 (cont'd)

- **Safety including**
  - Steroid-related AEs
  - Adrenal Suppression
  - Bone Metabolism/Growth
  - Serum bone metabolism biomarkers

- **Key Secondary Endpoints**
  - Changes in the PCDAI score
  - Changes in the number of patients without signs of Crohn's
  - Changes in the number of patients without abnormal Crohn's laboratory values
  - Changes in C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fecal lactoferrin, and fecal calprotectin
  - Changes in the IMPACT III Questionnaire score

Medical Advisory Board

- **Jeffrey Hyams, MD**
  - Head, Division of Digestive Diseases, Hepatology and Nutrition at Connecticut Children's Medical Center
  - Professor of Pediatrics at the University of Connecticut School of Medicine
- **James Markowitz, MD**
  - Professor of Pediatrics at Hofstra North Shore – Long Island Jewish (LIJ) School of Medicine, Division of Pediatric Gastroenterology and Nutrition at Cohen Children's Medical Center of NY North Shore – LIJ Health System
- **Joel Rosh, MD**
  - Associate Professor of Pediatrics at the University of Medicine and Dentistry of New Jersey
  - Director of Pediatric Gastroentereology at Goryeb Children's Hospital / Atlantic Health in Morristown New Jersey

SGX203 – Opportunity and Development Summary

SGX203 is a proprietary oral formulation of immediate and delayed release beclomethasone 17,21-dipropionate (BDP) tablets to treat GI inflammation with less toxicity than the current standard systemic steroid therapy

Market Opportunity

- **No approved drug for mild-to-moderate; unmet medical need**
- **Systemic steroids (unapproved) currently used as front-line; cause adrenal suppression, growth impairment, bone demineralization**
- **Oral BDP delivers high GI steroid effects with minimal (~35%) systemic side effects**
- **Remicade® and Humira® only approved products in Pediatric Crohn's in US – generally used after steroids fail**
  - **Both contain Black Box warning for increased risk of infection and potential malignancy (T cell lymphoma)**

Development Status

- **FDA Orphan Drug and Fast Track designations granted**
- **Active ingredient BDP FDA approved for over 40 years in other delivery forms (e.g., aerosol) to treat diseases such as asthma**
- **~350 subjects treated with oral BDP to date in multiple trials**
- **Pivotal Phase 3 adaptive trial in ~150 subjects ready to start**

Beclomethasone Dipropionate: Other GI Indications

SGX201 comprising delayed release beclomethasone 17,21-dipropionate (BDP) tablets to treat radiation toxicity to the small intestine, large intestine and rectum due to radiotherapy

Market Opportunity

- **Unmet medical need (granted fast track designation)**
- **~300,000 cancer patients receive pelvic radiotherapy annually in US and Europe**
- **After pelvic radiotherapy: 90% have altered bowel habit, 50% have reduced quality of life and 20-40% quality of life impact rated as moderate or severe**

Proposed Phase 2 Study Design

- **Prevention of radiation enteritis (RE) in women receiving pelvic radiation therapy for cancer**
- **Double-blind placebo-controlled randomized study comparing 5 mg BDP PO BID vs. placebo**
- **12 week efficacy phase followed by 12 month follow-up in ~80 subjects at 5-7 sites in the US**
- **Primary endpoint assessment based on Inflammatory Bowel Disease Questionnaire – Bowel: (IBDQ-B) (validated for pelvic radiation)**

Development Status

- **FDA Fast Track designation granted**
- **Initial study designed**

Intellectual Property and Market Exclusivity

- **Drug substance is well known (known to be safe) – no patent protection**
- **Method of use for proprietary 2-tablet, immediate and delayed release formulation of beclomethasone 17,21-dipropionate (Expiry: 2022)**
- **Method of use for proprietary 2-tablet, immediate and delayed release formulation of beclomethasone 17,21-dipropionate in radiation and chemotherapeutics injury (Expiry: 2029)**
- **Orphan drug application: 7 years market exclusivity (US)**

Key References

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