Ifetroban
Oral Thromboxane Receptor Antagonist for the treatment of Duchenne muscular dystrophy

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Disclosures

• No direct financial conflicts or disclosures
• PI for the clinical trial (no salary support)
• Specialty pharmaceutical company:
  – Developing products to address unmet medical needs
  – Headquarters in Nashville, TN
• Six marketed products:
  – Acetadote, Caldolor, Kristalose, Omeclamox, Vaprisol, Vibativ
• Ifetroban pipeline:
  – Cumberland is collaborating with multiple research centers to develop ifetroban for various orphan indications
  – Ongoing Phase 2 studies in systemic sclerosis and Samter’s triad (allergic disease)
  – 16 Phase 1 & 11 Phase 2 studies completed
    • healthy volunteers or patients with cardiovascular disease, acute renal injury, or portal hypertension

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Ifetroban

- A potent and selective antagonist of the thromboxane receptor (TPr)

- Ifetroban has or is being studied for unmet medical needs with no safety concerns identified to date

- Safety is well established
  - over 1,300 clinical trial participants
  - dosed in over 26 clinical studies
  - doses up to 1,000 mg without serious adverse events

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Ifetroban Blocks Thromboxane Receptor Signaling to Prevent Inflammatory Response & Fibrosis

Modified D’Amario et al. 2017
Ifetroban Blocks all Thromboxane Receptor Ligands from Activating Pro-fibrotic Pathways
Ifetroban
preclinical cardiac studies
Ifetroban prevents fibrosis & cardiac dysfunction in Pulmonary Artery Banding (PAB) Model of RV overload

West et al. Pulmonary Circulation 2016
Ifetroban improves cardiac function & survival in two severe DMD mouse Models

Carrier et al. Submitted unpublished
Ifetroban improves cardiac function & survival in limb-girdle md mouse model

A

Percent survival dSG KO

p = 0.0296

Age (months)

0 1 2 3 4 5 6

B

Fract Short (\%)

Eject Fract (\%)

Cardiac Index (mL/min/kg)

WT

dSG-veh

dSG-ifet

p=0.006

p=0.012

Carrier et al. Submitted unpublished
Ifetroban prevents cardiac fibrosis & blocks the pro-fibrotic TGF-beta pathway in LGMD mouse model

Carrier et al. Submitted unpublished
Ifetroban Clinical DMD Trial

About Ifetroban
Ifetroban belongs to a group of medicines called thromboxane receptor antagonists.
Ifetroban is an investigational drug with over 26 human trials and over 1,000 study participants treated.
DMD animal studies showed oral ifetroban can impact the heart disease associated with Duchenne and improve animal survival.
Ifetroban is available as oral capsules.

Who can participate?
To qualify for the trial, participants must:
- Be at least 7 years of age or older
- Have a documented diagnosis of DMD
- Be on a stable dose of steroidal corticosteroids for at least 10 weeks
- Have stable cardiac function defined as change in LVEF ≤ 0.05 or not more than 10% in the last 12 months, LVEF > 50% or greater by MUGA/CARD

Trial Design
The trial is randomized, double-blinded and placebo-controlled. Eligible participants will be randomized to 2 treatment groups: 2 dose levels of ifetroban or placebo. Each treatment group will enroll 8 participants with LVEF ≤ 40% and 8 participants with LVEF 35-40%. Participants who complete 12 months of treatment are eligible to participate in the open-label extension portion.
Each trial site is expected to be an average at 8-10 hours.

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Inclusion criteria:
General:
• Males 7+ yo with DMD diagnosis
• Stable dose of oral corticosteroids ≥ 8 weeks or no corticosteroids for ≥ 30 days

Cardiac measures:
• Stable cardiac function over the last 12 months
  • Defined as change in LVEF of < 15% and no heart failure admission
• LVEF 35% or greater by cine CMR or echo
• Myocardial damage evident by late gadolinium enhancement allowed

Medications:
• ACEI, BB, or ARB therapy allowed (selection dictated by clinical care)
  • Started 3 months or greater from first trial dose
• ARA (spironolactone or eplerenone) allowed
  • Started 12 months or greater from first trial dose

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Select Exclusion criteria:

- A LVEF of < 35% by CMR or echocardiography during screening

- Participants in a therapeutic clinical trial in last 30 days or five half-lives (whichever is longer) of study entry

- A known bleeding disorder or has received anticoagulant treatment within 2 weeks of study entry

- Allergy to gadolinium contrast or known renal insufficiency defined as abnormal cystatin C or creatinine above the upper limit of normal for age.

- Non-MR compatible implants (e.g. neurostimulator, automatic implantable cardioverter-defibrillator [AICD])

- Any other active medical condition that could interfere with study participation
Phase 2 Objective: evaluate efficacy, safety and PK of ifetroban in DMD
- Daily, oral ifetroban/placebo for 12 months; 2/3 of subjects randomized to ifetroban
- 3 visits in 12 months: CMR, PFT, QMT, QoL and 7-day actigraph
- Open-label extension available to all; placebo participants will receive ifetroban
Key assessments at baseline, Month 6 & Month 12 visits
- Cardiac MRI, PFT, Muscle Strength, Quality-of-life surveys, 7-day activity monitoring
- Day 0 PK completed within 4 hours at site using finger stick; 8-hr and 24-hr post-dose at home
- Day 7 PK completed at home: pre-dose and 30 minutes post-dose

Key eligibility and study features
- All DMD boys ≥ 7 yo regardless of mutation type, ambulation status & steroid use eligible
- No upper age limit
- Standard of care meds allowed including eteplirsen
- No biopsy or 6-minute walk test
Expected U.S. Locations:

- Riley (IN),
- Vanderbilt (TN),
- Nationwide (OH),
- CNMC (DC),
- Emory (GA),
- UCLA (CA),
- Yale (CT)

For more information: email: research@cumberlandpharma.com
PPMD FAQ site: https://www.parentprojectmd.org/faqs/ifetroban/

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