The combination of Ibuprofen and Isosorbide Dinitrate (ISOFEN): current clinical development

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CONNECT 20th ANNUAL CONFERENCE
26–28 June, Chicago, IL
Why we develop ISOFEN?

- To limit the use of corticosteroids
- To slow disease progression (to buy time)
- Applicable to all patients
- May be combined with gene/cell approaches (synergy)
- Cost-effective (affordable to the NHS)
nNOSµ is a component of the Dystrophin-Glycoprotein Complex directly interacting with α-syntrophin and caveolin 3

Myofibres express NOS III and a splice variant of NOS I (µ)

Nitric oxide synthase (NOS-Iµ) is absent from skeletal muscle sarcolemma in Duchenne muscular dystrophy.

• Overexpression of NOS-Iµ in the mdx mouse model ameliorates muscle dystrophy phenotype.

Bredt et al., 1995

Wehling et al., 2001
NO AND ADULT SKELETAL MUSCLE PHYSIOLOGY

NO regulates excitation-contraction coupling to prevent the muscle from being damaged during its contractile activity

- Regulating Ca\(^{2+}\) homeostasis, resting and action potential at neuromuscular synapses

NO couples energy supply with demand

- NO contributes to vasodilation, and thus supply of oxygen during exercise, and increases glucose uptake
- NO regulates enzymes relevant to cell energy metabolism (glyceraldehyde 3-phosphate dehydrogenase, aconitase, creatine kinase)

Wang et al., 1995; Bredt, 1998; Stamler and Meissner, 2001; Nisoli et al., 2004
NO triggers myogenic precursor cells activation

(Anderson, 2000)

NO enhances the ability of myogenic precursor cells to fuse to damaged myofibres

(De Palma and Clementi, 2012)

NO stimulates myogenic differentiation acting on bioenergetics of the cells

(De Palma et al., 2010)

NO maintains the pool of myogenic precursor cells preventing their exhaustion during damage repair

(Buono et al., 2012)

NO interacts with key myogenic pathways (HDAC signalling; miRNA, Wnt)

(Colussi et al., 2008; Cacchiarelli et al., 2010; Buono et al., 2012)
Progressive damage to muscle tissue

**Early DMD**
- Little connective tissue
- Regular fiber shape
- Few dying muscle fibers

**Later DMD**
- Much more connective tissue, fat
- Irregular fiber shape
- Many dying/regenerating fibers

*Worton et al, 2001*
Muscular Dystrophy and NO-NSAIDs

- Brunelli et al., PNAS 2007
- Sciorati et al., Br. J. Pharmacol, 2010
- Sciorati et al., Pharmacol Res, 2011
- Sciorati et al., Pharmacol Res, 2013

HCT 1026
NCX320
NCX701
NCX6550
Naproxcinod

**ISOFEN**
(Ibuprofen plus ISDN)
ISOFEN AND MUSCLE REPAIR
THE PRECLINICAL EVIDENCE

Sciorati et al., Br. J. Pharmacol, 2010
ISOFEN is active on the dystrophic heart

Sciorati et al., 2013
Effect on fibrosis

Study duration: 18 months: 6-8 months enrollment, 12 months treatment period

Graph: Effect on myocardial interstitial collagen content (% of area)

- WT
- Untreated
- IBU+ISDN

Images: Comparison of myocardial interstitial collagen content between untreated and treated groups.
Preliminary study in patients

Nitric oxide donor and non steroidal anti inflammatory drugs as a therapy for muscular dystrophies: Evidence from a safety study with pilot efficacy measures in adult dystrophic patients

Maria Grazia D’Angelo, Sandra Gandossini, Filippo Martinelli Boneschi, Clara Sciorati, Sara Bonato, Erika Brighina, Giacomo Pietro Comi, Anna Carla Turconi, Francesca Magri, Giuseppe Stefanoni, Silvia Brunelli, Nereo Bresolin, Dario Cattaneo, Emilio Clementi
Adverse events recorded during the study

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total</th>
<th>DMD</th>
<th>BMD</th>
<th>LGMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache(^{a})</td>
<td>19</td>
<td>6</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Precordial pain (negative cardiological check)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Epigastric pain(^{b})</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Lower limbs edema</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
<td>5</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Meteorism, digestive disturbances</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

DMD = Duchenne Muscular Dystrophy; BMD: Becker Muscular Dystrophy; LGMD = Limb-Girdle Muscular Dystrophy.

\(^{a}\) 17 patients present very mild headache, at the beginning of the treatment, with spontaneous decreased in one week.

\(^{b}\) Advantage from increase of pantoprazole from 20 to 40 mg/day.
Differences of MFM D1 between the 12-month follow-up and baseline in placebo and drug-active patients
COMBINATIONS ISOSORBIDE + IBUPROFEN: DEVELOPMENT STRATEGY

- **ISOFEN 1**: Pharmacokinetics Study in Healthy Volunteers to assess pharmacokinetic parameters- completed

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ISOFEN1 TRIAL: Pharmacokinetics of isosorbide
ISOFEN1 TRIAL: Pharmacokinetics of ibuprofen

![Graph showing pharmacokinetics of ibuprofen and ibuprofen+isosorbide](image-url)
### ISOFEN 1 TRIAL: safety profile

<table>
<thead>
<tr>
<th></th>
<th>Isosorbide</th>
<th>Ibuprofen</th>
<th>Isosorbide plus Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment-related AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of events in subjects (%)</td>
<td>9</td>
<td>0</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>7 (58.3%)</td>
<td>0</td>
<td>3 (33.3%)</td>
</tr>
<tr>
<td><strong>Intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>8 (80%)</td>
<td>0</td>
<td>4 (100%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (20%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
COMBINATIONS ISOSORBIDE + IBUPROFEN: DEVELOPMENT STRATEGY

- **ISOFEN 1**: Pharmacokinetics Study in Healthy Volunteers to assess pharmacokinetic parameters. *completed*

- **ISOFEN 2**: Human Pharmacology to select the optimal and safe dosage regimen for Isosorbide and Ibuprofen in healthy volunteers. *completed*
ISOFEN2 TRIAL: Study objectives

**Primary**
- To select the maximum tolerated dose for ISO when co-administered with IBU. In particular that the combination of IBU 200 mg with ISO up to 80 mg/d is well tolerated by at least the 80% of the subjects

**Secondary**
- To assess the safety in terms of AE
- To assess the Blood Pressure variation during the trial
ISOFEN2 TRIAL: Study Design

V2 baseline

V3 5-7 days

V4 10-14 days

V5 15-21 days

IBU 200 + ISO 80

IBU 200 + ISO 60

IBU 200 + ISO 40

IBU 200 + ISO 20

If DBP > 60 mmHg increase dose

If DBP < 60 mmHg maintain actual dose

If DBP > 60 mmHg increase dose

If DBP < 60 mmHg maintain actual dose

If DBP > 60 mmHg increase dose

If DBP < 60 mmHg maintain actual dose

*DBP: diastolic blood pressure
ISOFEN2 TRIAL: 
Results

20 Healthy free-living subjects screened

1 subject voluntarily reduced the dose of ISO to 60 mg/day

18 subjects completed the study tolerating the maximum dose of ISO (80 mg/day)

1 subject did not fulfill inclusion criteria
ISOFEN2 TRIAL: Results

✓ AEs were mild/moderate and resolved without any concomitant treatment.

✓ Some subjects reported transient episodes of headache in the first days of treatment. All episodes resolved spontaneously after the first week of therapy.

✓ No AEs lead to discontinuation and no Serious Adverse Events (SAEs) occurred during the study.
COMBINATIONS ISOSORBIDE + IBUPROFEN: DEVELOPMENT STRATEGY

- **ISOFEN 1**: Pharmacokinetics Study in Healthy Volunteers to assess pharmacokinetic parameters. *completed*

- **ISOFEN 2**: Human Pharmacology to select the optimal and safe dosage regimen for Isosorbide and Ibuprofen in healthy volunteers. *completed*

- **ISOFEN 3**: Safety and Efficacy Evaluation of the drug combination in Duchenne Patients in a multicentre, randomised, double-blind, dose titration phase II clinical trial. *To be started soon*
Primary Objective
efficacy of the combination of ibuprofen and isosorbide dinitrate in delaying the worsening of the muscular motor function in patients with Duchenne muscular dystrophy assessed by PUL scale.

Secondary Objectives
Safety and tolerability
Efficacy assessed by other cardiac and pulmonary measures of functionality, and quality of life through a questionnaire
**ISOFEN 3 objectives**

**Cardiac Function:**
- Change in peak systolic radial strain left ventricle (LV) inferolateral wall (%)
- Change in peak systolic radial strain rate LV inferolateral wall (%)
- Change in peak systolic longitudinal strain LV lateral mid (%)
- Change in Ejection Fraction (EF) (%)
  - Change in Fractional Shortening (FS) (%)

**Pulmonary function:**
- Change in Peak Cough Flow (%)
- Change in Maximum Expiratory Pressure (MEP) [cm H20] and MEP predicted (%)
- Change in Maximum Inspiratory Pressure (MIP) [cm H20] and MIP predicted (%)
- Change in FVC [L] and FVC predicted (%)
  - Change in FEV1 [L] and FEV1 predicted (%)

**Quality of life:**
- Paediatric Quality of Life Inventory TM (PedsQL)
ISOFEN 3 Subjects and Centres

NUMBER OF SUBJECTS:

Sample size: 208 patients in the two arms based on the mean change (%) of the PUL scale from baseline to the end of the study, a value of efficacy (% predicted) of -3.0 an alpha level of 0.05, a power of 70%, a drop out rate of 10%

NUMBER OF STUDY CENTRES: 10
ISOFEN 3 main inclusion criteria

written informed assent and parents/guardians written informed consent: 2. Confirmed diagnosis of Duchenne muscular dystrophy

Age ≥ 6 years

Patients non-ambulant (at least 1 year in a wheelchair) within the last 4 years

Patients who receive the standard of care for Duchenne muscular dystrophy

Patients on chronic glucocorticosteroid treatment: dosage must be stable in the 6 months prior to the anticipated first administration of study medication
ISOFEN 3 main exclusion criteria

Any acute co-morbid condition interfering with the well-being of the patient

A left ventricular ejection fraction (EF) of < 30%
Forced vital capacity (FVC) < 40% of predicted
History of recurrent headache

History or presence of allergy or intolerance to the study drugs

Previous or ongoing medical conditions, medical history, physical findings or laboratory abnormalities that could affect safety

Weight of less than 13 kilograms
study duration will be of 36 months divided as following:

Enrolment: 6 months

Longitudinal observation period: 12 months

Treatment period: 18 months
ISOFEN 3 funding

Total cost: €1,250,000

Already available: €500,000 from the EU 7th framework programme

Pledged by Duchenne Alliance: €350,000

Still needed: €400,000 with PP Italy playing a major role in fundraising