Meta–IQ

Etomoxir for the treatment of Multiple Sclerosis and Depression
The company

- Meta-IQ develops Etomoxir for the treatment of Multiple Sclerosis and Depression.
- The Multiple Sclerosis market exceed 5 Billion USD per year and the depression market exceed 12 Billion USD per year.
- Meta-IQ is ready to initiate phase II clinical trials in Multiple Sclerosis and depression.
- Etomoxir is a selective and irreversible inhibitor of CPT-1 which reset the energy metabolism from fatty-acid back to glucose resulting in neuroprotective and anti-inflammatory properties.
- Etomoxir has shown superior effects in the EAE animal model of Multiple Sclerosis
- Etomoxir has shown superior effect in the chronic mild stress model of depression
- Etomoxir is safe and has already passed several clinical trials in other indications with more than 500 patients and healthy volunteers.
- Meta-IQ has secured the relevant intellectual property with protection until 2029.
Management of Meta-IQ

- Jette G. K. Nieland, CEO, MSc in clinical and business psych. Responsible for financial and business development

  She has 20 years of experience in working with brain diseases, 6 years in biotech and 12 years in management

- John D. Nieland, COO, Assoc. prof. biotech., Ph.D. in medicine. Responsible for research and organization of clinical trials

  He has 20 years of experience in working with biotech, 10 years as director of research and in management

- We collaborate with different experts in the field on all levels of business as well as research
Business collaboration possibilities

- Sale of assets of Meta–IQ to an interested partner with the possibility of consulting support

- Investment collaboration, where Meta–IQ develops the medicine in a clinical phase 2 trial in MS and/or Depression

  - For the development of the medicine in MS a 1.9 Mill € support of Neu2 in Germany is approved. The company has to be established in Germany

  - Alternatively the company can develop both Depression and MS in Denmark or other countries
Meta-IQ is ready to initiate two clinical phase II trials in Multiple Sclerosis:
- 6-month study with 12-month follow-up in Optic Neuritis
- 18-month study in Secondary Progressive Multiple Sclerosis

Meta-IQ has been approved for 1.9 million € financial support from NEU², Germany in May 2012.

Meta-IQ is seeking a total investment of 9 m€ in order to conduct these two clinical trials within a period of 3 years.
Current development status and plan in Depression

- Meta–IQ is ready to start a phase 2 clinical trial in Depression
  - 200 patients with moderate to severe depression.
  - 40 or 80 mg/day Etomoxir and placebo or standard medication
  - Study duration 2 month with a 4 month follow up

- Meta–IQ is seeking an investment of 6 m€ in order to conduct this clinical trial within a period of 2 years
Lipids in the brain and neuroprotection (1)

Palmitate coupled to Myelin is the isolation around nerve cells. It secures signaling speed and efficiency, and it shields the myelin protein from immune recognition. When fat metabolism is activated the myelin protein is exposed to the immune system and signaling capacity and speed decrease.

Blocking fatty acid metabolism reverts the disease inducing cascade.
The half-life of palmitate bound to myelin is 3 days.

Palmitate bound to myelin form the myelin sheath that isolate nerve cells.
  - This complex makes signal transmission go faster and more efficient and with less energy loss.

With prolonged stress lipid levels in the brain locally decrease.

CPT-1 which is the rate limiting step in fatty acid metabolism is up-regulated in a number of inflammatory conditions (including Multiple Sclerosis) in the brain.
Fatty acid metabolism and anti-inflammatory effects

- During prolonged stress (Physical, psychological or due to infections) the oxygen supply is down-regulated

- Under low oxygen levels the fat metabolism is incomplete

- Fatty acid metabolism intermediates end up in the PGE2 synthesis pathway

- PGE2 attract and activates the immune system locally

- Blocking fatty acid metabolism blocks the attraction and activation of the immune system locally and thus has anti-inflammatory effects
Mechanism of action

External causes

- Oxidative stress

Glucose metabolism

- Fatty acid metabolism

- Free radical formation

- Decrease of fatty acids

- Demyelination

- Exposure of axons
- Activation of immune system

Etomoxir

- PGE 2 activation
- Free radical formation
- Decrease of fatty acids

Proprietary information from Meta-IQ
MS is induced by an injection of a myelin protein, MOG35–55, together with complete Freuds adjuvans.

Animals are treated at day 8 and 15 after induction of MS with a one time injection of 15mg/kg Etomoxir or placebo i.p.
EAE model of Multiple Sclerosis

Blue are cell nuclei
Green is myelin protein

Nature Scientific reports, September 2011
EAE model of Multiple Sclerosis

Red are T cells

Green are CD11b\textsuperscript{+} macrophages and microglial cells

Nature Scientific reports, September 2011
EAE model of Multiple Sclerosis

Nature Scientific reports, September 2011

Proprietary information from Meta-IQ
EAE model of Multiple Sclerosis

% Disease free animals

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<th>Etomoxir</th>
<th>Placebo</th>
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Data from Meta-IQ/BRIC Copenhagen
Anti-inflammatory proof of concept (POC) (1)
IFNγ specific T cell response is down-regulated

Left picture Meta-IQ experiment (BRIC) 2 week treatment 1 mg/kg/day sc. Injection,
right UCSD 2 week treatment 15mg/kg/week i.p. injection
T cells were taken from animals at end of 2 week treatment period
Etomoxir against Depression

- Depression can develop after chronic stress
  - Best predictive animal model is chronic mild stress

- Stress induce switch to fatty acid metabolism from glucose metabolism

- Stress increase cortisol levels and increased cortisol levels can lead to depression (Cushings disease)
  - Cortisol delays remyelination

- Depression severity is correlated to prefrontal cortex hypofunction

- In an animal model of depression, social isolation, a loss in myelination in prefrontal cortex is observed (Nature Neuroscience, November 2012)

- Meta-IQ has shown that Etomoxir reverse depression in the chronic mild stress model in just one week (all other drugs need 4 weeks before an effect is seen)
Chronic mild stress model of depression

Dr Ove Wiborg, Aarhus University, Denmark
Etomoxir in memory loss

1 day treatment with MIQ 001 restores memory

% animals with restored memory

Long term memory
Short term memory

0 20 40 60 80

Dr Ove Wiborg, Aarhus University, Denmark
Depression market

- The market against depression is over 12 Billion US $

- The market is dominated by SSRI and SNRI compounds which are only effective against mild to moderate depression

- Beneficial effects are not seen before 4–6 week of treatment
  - Major concern on suicide attempts in this period

- A drug which induce an effect against depression following only 1–2 weeks may obtain huge market shares

- No effective drug exists against severe depression
  - Best treatment is Electro–Convulsive Therapy

- A drug which induce any beneficial effect against severe depression may open a whole new market
Summary Results in CNS disorders

- **Multiple Sclerosis**
  50% of the diseased animals are cured within 2 weeks of treatment
  Results independently confirmed by UCSD scientists

- **Depression**
  Beneficial effects are seen in 70% of the diseased animals within one week of treatment and up to 95% after a 4 week treatment

Drugs on the market maximally achieve visible effects in 50% of the treated patients after 4 – 6 weeks of treatment
Main Findings of Preclinical Studies

- No genotoxic potential
- No toxicity in reproductive experiments
- No safety issues in pharmacology studies
- Repeated dose studies: effects at > 5 mg/kg oral dose (rat)
  - Target organs: liver, kidney, heart
Etomoxir

- (R)-(+)–Ethyl 2[6–(4–chlorophenoxy)hexyl]–oxirane–2–carboxylate
- Target: Carnitine–Palmitoyl Transferase I (IC$_{50}$ of low nM)
- Etomoxir enters easily the brain
- Half-life of 34 hours (gamma phase)
- The material is highly stable at room temperature.
- 35Kg of GMP material is available and stored at our manufacturer
## Intellectual Property

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<tr>
<th>Patent No.</th>
<th>Filing date</th>
<th>Country</th>
<th>Status</th>
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<tr>
<td>WO 2009/156479</td>
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<td>The use of fatty acid oxidation blockers for the treatment and prevention of disorders caused by delipidation of neuronal tissue</td>
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<td>Priority: 06/27/2008 (US)</td>
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<td>Inventors: Nieland</td>
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<td>EP 2310003</td>
<td>06/25/2009</td>
<td>EP (all member states)</td>
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<td>06/25/2029*</td>
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<td>US 13/001,422</td>
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<td>AU 2009264237</td>
<td>06/25/2009</td>
<td>AU</td>
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<td>06/25/2029*</td>
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<td>CA 2,766,282</td>
<td>06/25/2009</td>
<td>CA</td>
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<td>06/25/2029*</td>
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| WO 2002/079178   |             |                       |         |                   |
| Methods for producing oxiran carboxylic acids and derivatives thereof |
| Priority: 03/30/2001 (DE) |
| Inventors: Cernerud, Berntsson |
| EP 1373237       | 03/28/2002  | EP (AT DE FR GB LU SE TR) | issued  | 03/28/2022*      |
| DE 10115938      | 03/30/2001  | DE                    | pending | 03/30/2021*      |
| US 7,078,543     | 03/28/2002  | US                    | issued  | 03/28/2022*      |

* Expiry dates are provided without potential patent term extensions
Preclinical Proof of concept (POC) reached
Proof of concept for Multiple Sclerosis and Depression has been reached

Clinical trials in MS and other brain diseases
Phase I trial in healthy volunteers finished

Pre-clinical development, Pharm/Toxic studies completed
Toxicity pharmacology package is complete to start human clinical phase II trials

POC data in Multiple Sclerosis independently confirmed
In September 2011 the group of Manchester of the University of California, San Diego has independently confirmed the data generated by Meta–IQ in MS previously. The results are published in The Nature publishing group journal Scientific Reports

Intellectual property rights secured
Granted patents for synthesis, US patent application for use and a PCT application for the treatment of brain and other diseases which will give protection until 2029. The relevant rights have been in-licensed or have been filed by Meta–IQ

Manufacturing process established
Active Pharmaceutical ingredient (API) is available at GMP-grade (Good Manufacturing Praxis)

Financing of clinical trials in MS
May 2012 Meta–IQ has been approved by the Neu2 Consortium, Germany for financial support of up to nearly €2 Million of the further development cost of MIQ for patients suffering from Multiple Sclerosis