Repositioning of the drug CBG000592 for treatment of ischemic stroke

A novel mechanism of neuroprotection: Blood glutamate grabber.

José Castillo & Francisco Campos
Content

1. The Institution and the actual pipeline

2. The Product
   - Target Indications
   - Innovative aspects
   - Current status of development: proof of concept and trials already performed
   - Differential features facing the market and business opportunities
   - IPR protection
   - Pitfalls & Risks to be considered
1. The Institution and the actual pipeline

- Over 700 researches
- 1700 Scientific articles
- 455 publications
- More than 46 patents since 2009
- 14 M€

Innovation and knowledge transfer in 2013:

- 24 Patents
- 2 Licenses
- 10 National
- 13 International
- 2 National, 2 International
- 3 National, 9 International

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1. The Institution and the actual pipeline
2. The Product

**ARTERIAL OCCLUSION**

- Energetic failure
- Excitotoxicity (Glutamate)
- CBF
- Gene expression
- Inflammation
- Oxidative stress
- Apoptosis

*Expected benefits*

**Time**

**ARTERIAL OCCLUSION**

- Energetic failure
- Excitotoxicity (Glutamate)
- CBF
- Gene expression
- Inflammation
- Oxidative stress
- Apoptosis

*Expected benefits*
2. The Product


- NMDA receptor blockade at glycine site
- AMPA antagonist
- Non-competitive NMDA channel blocker
- Competitive NMDA receptor blocker
- NMDA polyamine site blocker
- NMDA co-agonist

- Patients

Clinical trials

- NMDA receptor blockade at glycine site: 6
- AMPA antagonist: 6
- Non-competitive NMDA channel blocker: 4
- Competitive NMDA receptor blocker: 2
- NMDA polyamine site blocker: 1
- NMDA co-agonist: 1
- Patients: 6.091
2. The Product

![Diagram showing the changes in blood-glutamate levels under different conditions.](image)

- **Physiological condition**
  - Blood-glutamate barrier
  - Brain: 15 µM
  - Blood: 100 µM

- **Cerebral ischemia**
  - Brain: 200 µM
  - Blood: 300 µM
  - BBB disruption

- **Hypothesis**
  - Blood-glutamate grabber

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**VII Encuentro de Cooperación Farma-Biotech**
2. The Product

BRAIN
GLUTAMATE

PLASMA
GLUTAMATE

BioFarma
Innnopharma

Compound Code (among 1114 drugs) | IC$_{50}$ (µM)
---|---
CBG000592 | 4.04

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2. The Product

Preclinical phase

In vivo (model of ischemia/reperfusion)

- Control (saline)
- CBG000592, 1 mg/kg
- Oxaloacetate, 35 mg/kg
- CBG000592+Oxal, 15 mg/kg

Lesion volume (mm$^3$)

- Basal - DWI
- 24 h - T2
- 7 D - T2

Plasma glutamate (µM)

- Basal
- 1 h
- 3 h
- 24 h

* $p<0.05$
** $p<0.001$

relative to the control group

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2. The Product

The efficient (determined as lesion volume at 7 days) of the different blood glutamate grabber is similar, therefore election of the treatment depends on their safety.
2. The Product: Target Indications

9. FETAL ASPHYXIA. Article in progress.
2. The Product: Target Indications

2. The Product: Innovative aspects vs previous treatments.

1. It does not require a prior computerized tomography scan therefore, it could be given as early as possible, perhaps even as ambulatory treatment suggesting potential clinical application.

2. It is not mediated through the neuronal ionotrophic glutamate receptors, thereby avoiding problems of poor blood–brain barrier permeability and potential neurotoxic effects.

3. The effect of the mechanism is not much longer than 24 h, as serum glutamate concentrations come back to normal within the first 6 h, which reduces long-term potential adverse effects.
2. The Product: Current status of development: proof of concept and trials already performed
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Randomized clinical trial with two parallel groups, double-blind and placebo-controlled to investigate if administration of CBG000592 in patients with acute ischemic stroke causes a reduction of glutamate-mediated excitotoxicity.

EudraCT number: 2014-003123-22
Product: CBG000592
Sponsor: José Castillo, MD, PhD.

Inclusion criteria:
1. Patients with suspected stroke in 3 hours of onset.
2. Age $\geq$ 18 years.
3. Informed consent signed.

Arm A (control): single IV bolus administration of placebo (sterile 0.9% sodium chloride), 25 patients. Or Arm B (experimental): single IV bolus administration of CBG000592, 25 patients.

Termination date of the enrollment period: June 2015. Study completion date: December 2015.

Clinical trial: proof-of-concept.
National, single-center, parallel, randomized, double-blind and placebo-controlled clinical trial to investigate if CBG000592 IV administration -20 mg (bolus)- in patients with acute ischemic stroke, produces variations in serum glutamate levels.

Principal objective:
- Study if the CBG000592 administration in patients with ischemic stroke induces a reduction of glutamate-mediated excitotoxicity levels.

Secondary objectives:
1. Explore if patients with ischemic stroke treated with CBG000592 have an average stay in hospital lower than who received placebo.
2. Explore if patients with ischemic stroke treated with CBG000592 have a higher percentage of clinical improvement than who received placebo.
3. Explore if patients with ischemic stroke treated with CBG000592 have a better functional outcome measure than who received placebo.
4. Investigate variations in serum glutamate curves between patients who were treated with placebo or CBG000592.
5. Explore the prognosis between patients who receiving treatment with CBG000592 or placebo and have no stroke.
6. Study the safety of treatment with CBG000592.
2. The Product: Differential features facing the market and business opportunities


119 studies from 119 countries


Projection of the distribution of incident stroke


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2. The Product: Differential features facing the market and business opportunities


rtPA

< 10 % Patients

Projection of the distribution of incident stroke


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2. The Product: Differential features facing the market and business opportunities

2. The Product: IPR protection

*CBG000592* in combination with oxaloacetate for stroke treatment, has not been either patented or published, until clinical results.
2. The Product: Pitfalls & Risks to be considered

1. CBG000592 is already commercialized

2. Clinical trial.
   1. CBG000592 has been used previously in humans, therefore human toxicity analysis (Phase I and II) are not needed before to test its effects in stroke patients.
   2. Successful results in patients will demonstrate that the mechanism proposed is effective for stroke.
   3. Reduce the investment risk for future trials based on the use of new treatments with blood glutamate grabber activity for stroke.