Programa Cooperación Farma-Biotech

9º encuentro (4 de julio de 2013)

NST0037, a novel statin with an improved neuroprotective profile

NEURON BIOPHARMA

Barcelona, 4 de julio de 2013

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
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2. The Product
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   c) Differential features facing the market
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   f) Pitfalls & Risks to be considered
3. Partnering Opportunities

A leading Spanish biotechnology company

- **Neuron Bio** started its business at the end of 2006 as an Spin-off from the Autonomous University of Madrid.
- Since July 2010, **Neuron Bio** has been quoted on the Spanish Alternative **Stock Market** (MAB).
- **Neuron Bio** owns 50% of **Neol**, a joint venture with **Repsol.**
- Its team currently includes 25 full-time staff (17 involved in R&D) working in *circa* **800 m²** facilities (labs, offices). A new building will be available during 2013.
- **Neuron Bio** holds the Certificate of Quality for R&D Management **(UNE 166.002).**
- **Neuron Biopharma** is a division of the Neuron Bio group, focused in R&D for neurodegenerative diseases.
- **Neuron Bio** develops their projects with own founds and founds from different Spanish (CDTI and CTA) and European programs.

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MISSION

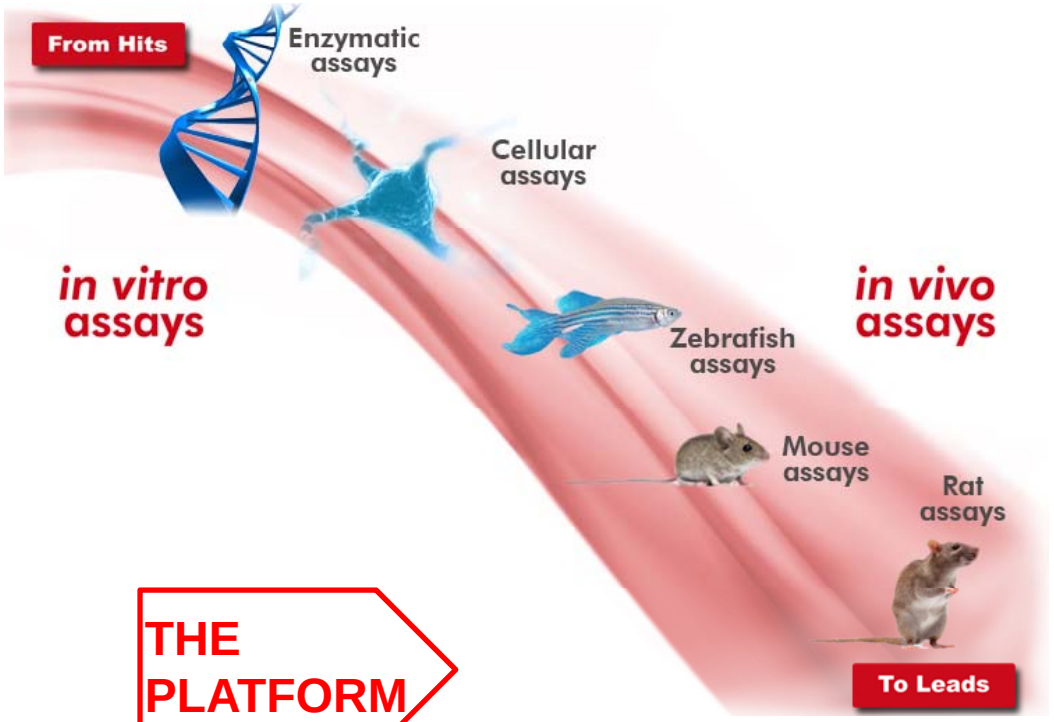
Neuron Bio's main goal is working on the discovery and development of compounds which help to prevent **several neurological** and **neurodegenerative diseases**.

Research on **Alzheimer's disease (AD)** is the main aim of this division, which concentrates on understanding the implications of the **regulation of cholesterol in the brain**. Neuron Bio approaches this kind of disease from the prevention angle, focusing on the **early stages of the disease**.

The search of **biomarkers** for AD is a secondary scope of the company

NEURON BIO'S CORE CAPABILITIES

CHEMICAL DIVERSITY



THE PLATFORM

THE PIPELINE

TOWARDS THE PATIENT

The origin of Neuron Statin Project

Long-term prospective population-based studies have indicated that elevated **cholesterol levels in midlife increase the risk of AD** in later life

In experimental models, **high cholesterol increases Aβ production**

Several **risk factors for AD are associated with cholesterol** metabolism, including dyslipidaemia and coronary artery and cerebrovascular disease

A relationship between alterations in cholesterol homeostasis and Alzheimer's disease (AD) has been reported for more than 10 years

Polymorphisms in **apolipoprotein E** (apoE) and other proteins involved in cholesterol metabolism are risk factors for AD

Previous treatment with **statins reduces the risk of developing AD**

Designing statins with greater neuroprotective activity

STEP 1. Analysis of statins used in humans to identify the best neuroprotectant of the series, thus defining the starting point of the project

Sierra S, Ramos MC, Molina P, Esteo C, Vázquez JA, Burgos JS. Statins as neuroprotectants: a comparative in vitro study of lipophilicity, blood-brain-barrier penetration, lowering of brain cholesterol, and decrease of neuron cell death. **J Alzheimers Dis**. 2011. 23: 307-318.

Ramírez C, Tercero I, Pineda A, Burgos JS. Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxity and memory impairment. **J Alzheimers Dis**. 2011. 24: 161.

Ramos MC, Sierra S, Ramírez C, Velasco J, Burgos JS. Simvastatin modulates the Alzheimer´s disease-related gen seladin-1. **J Alzheimers Dis**. 2012. 28 (2): 297

STEP 2. Identification of critical points in the molecular structure/shape related to neuroprotection

STEP 3. Design & synthesis of novel, patentable statins with strong neuroprotective characteristics

Campoy S, Sierra S, Suarez B, Ramos MC, Velasco J, Burgos JS, Adrio JL. Semisynthesis of novel monacolin J derivatives: hypocholesterolemic and neuroprotective activities. **J Antibiot**. 2010. 63 (8): 499

STEP 4. Identification of the best candidate of the new series and preclinical evaluation in translational AD models

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PIPELINE

SCREENING	EFFICACY	REGULATORY	PHASE I	PHASE II

NST0003, 04 & 05 → **P200900718** : "Compuestos neuroprotectores".

NST0037 → **EP09382051.2** : "Compuesto neuroprotector, hipocolesterolémico y antiepiléptico".

NST0060 → **P201001340:** "Compuesto neuroprotector, hipocolesterolémico, antiinflamatorio y antiepiléptico".

NST0076 & 78 → **P201330844**: "Compuestos neuroprotectores, anti-inflamatorios y antiepilépticos".

Neuron Bio has discovered & developed a family of novel neuroprotective statins with several characteristics (CNS penetration, antiepileptic potential, anti-inflammation…)

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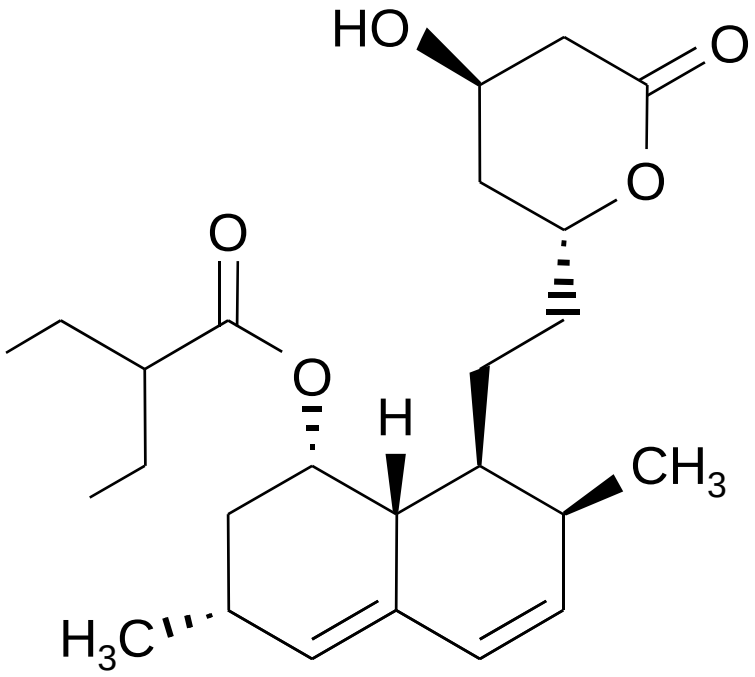
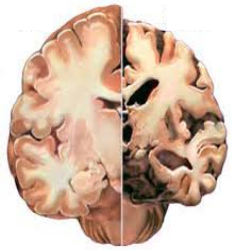
The product

NST0037



TARGET INDICATIONS

Alzheimer disease (MCI-to-AD)



Preclinical platform
Neuroprotection

↓

Acute
Neurodegeneration/Epilepsy

↓

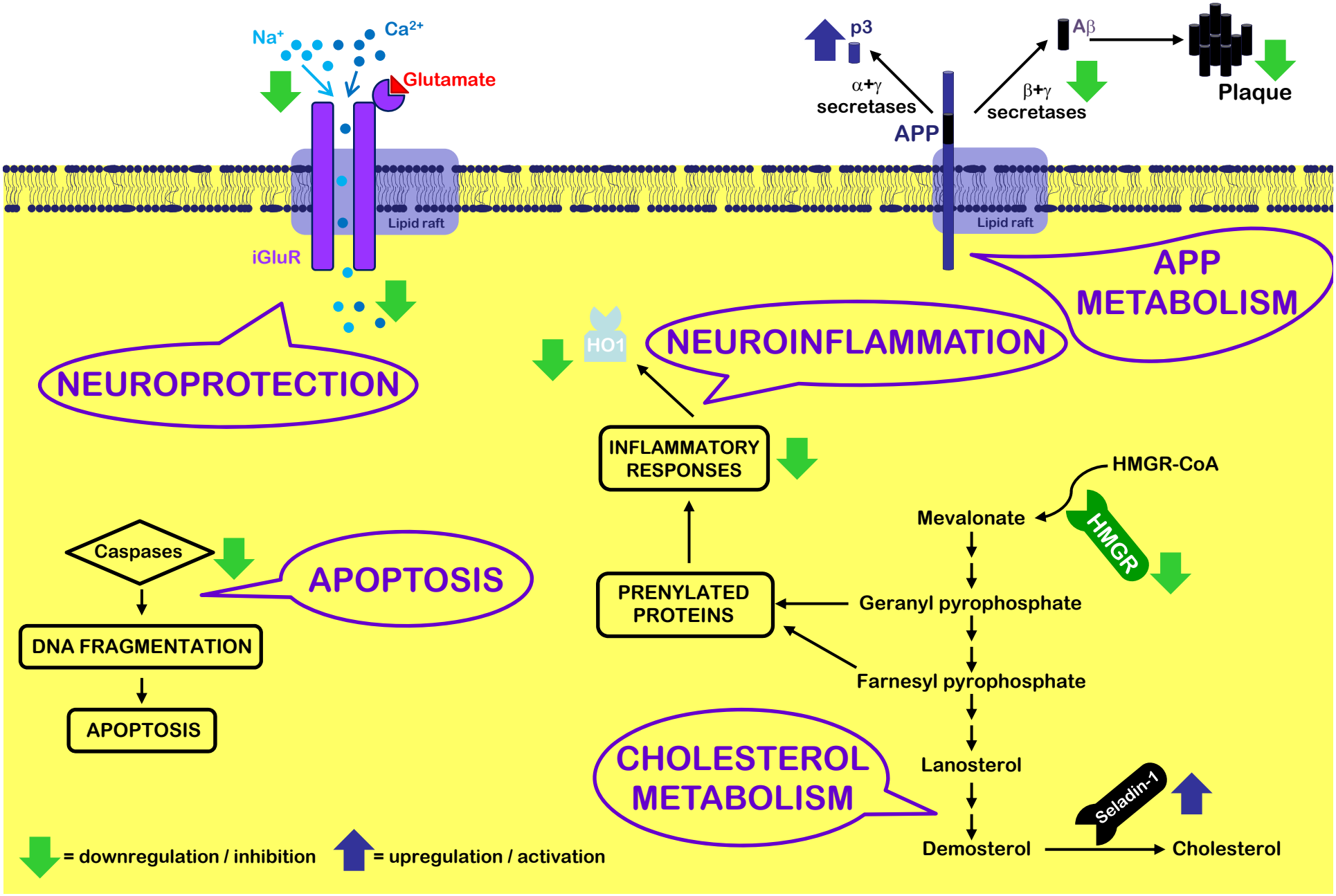
NST0037

AD Indication
Chronic neurodegeneration
Induced models
Transgenic models

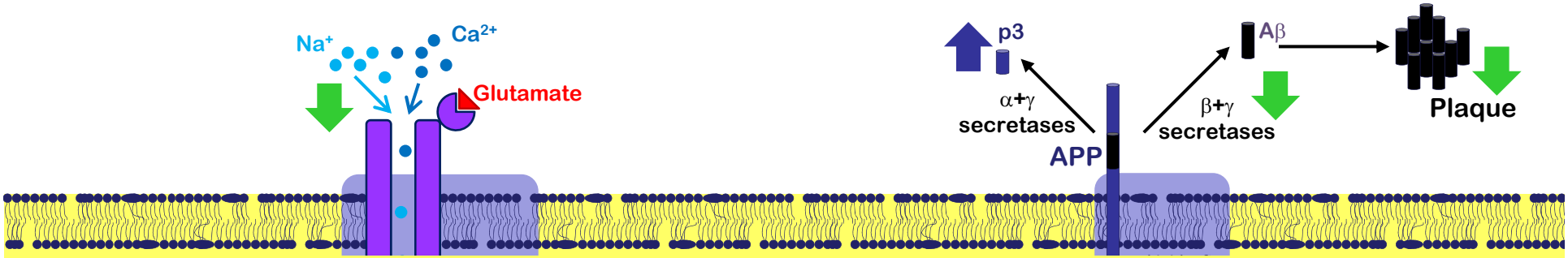
Epilepsy

Patent of use (statins)
Safety profile
Potent anticonvulsant effect
Better antiepileptic than simvastatin
Easier clinical development
High objective market

MECHANISMS OF ACTION



MECHANISMS OF ACTION



NEUROPROTECTIVE
ANTI-EPILEPTIC

NST0037

HYPOCHOLESTEROLEMIC

ANTI-INFLAMMATORY

CURRENT STATUS OF THE DEVELOPMENT

SCREENING	EFFICACY	REGULATORY	PHASE I

NST0037

- ✓ Neuroprotection
- ✓ Hypocholesterolemia
- ✓ Inflammation
- ✓ Mechanism-of-action
- ✓ Brain access

- ✓ Neuroprotection
- ✓ Epilepsy
- ✓ Hypocholesterolemia
- ✓ Inflammation
- ✓ Long-term studies
- ✓ Pharmacokinetics

- ✓ Chemical development
- ✓ Pharmacodynamics
- ❖ Toxicology
- ❖ Pharmacokinetics & metabolism
- ❖ Safety pharmacology

- ✓ First-in-human design
- ❖ Tablet production
- ✓ API production
- ☐ First-in-human trial

✓ Completed

❖ Ongoing

CURRENT STATUS OF THE DEVELOPMENT

CMC

Drug substance

- ✓ Synthesis proccess
- ✓ Analytical development
- ✓ 15 batches (up to 7.5 kg)
- ✓ Reference standard available
- ✓ Compound characterization
- ❖ Short-term excursions

Drug product

- ✓ Tablet formulation
- ✓ Analytical development
- ❖ Pilot batch synthesis

✓ Completed
❖ Ongoing

CURRENT STATUS OF THE DEVELOPMENT

PRECLINICAL DEVELOPMENT: NEUROPROTECTIVE EFFECT

Animal models
1. Acute neuronal death model
2. Chronic neuronal death model
3. Transgenic AD model

Translational biomarkers

- Strong neuroprotective effect: neuronal death and damage (H&E and MAP-2)
- Strong anti-epileptic effect
- Strong antiapoptotic effect (TUNEL)
- Prevents early neurodegeneration (SOM and NPY)
- Reduces senile plaque load
- Preserves cerebral metabolic activity (^{18}PET-FDG)
- Reduces cognitive decline (MWM)
- Reduces peripheral (TNFα and IL-6) and central inflammation (astrogliosis, microgliosis, Ho-1 expression, cD11b, TNFα, IL-1β)

CURRENT STATUS OF THE DEVELOPMENT

PRECLINICAL DEVELOPMENT: HYPOCHOLESTEROLEMIC EFFECT

Animal models

1. **Acute pharmacologically induced models of hypercholesterolemia**
2. **Atherogenic-diet induced models of hypercholesterolemia in guinea pigs**
3. **Transgenic models of hypercholesterolemia**

- Acute hypocholesterolemic effect in a pharmacologic model of hypercholesterolemia (24h)
- Acute and subchronic hypocholesterolemic effect in transgenic mice (12h, 28 days and 3 months)
- Chronic hypocholesterolemic and hypotriglyceridemic effect in transgenic mice consuming atherogenic diet (7 months)
- Subchronic hypocholesterolemic effect in guinea pigs consuming atherogenic diet (28 days)

CURRENT STATUS OF THE DEVELOPMENT

PRECLINICAL DEVELOPMENT: ANTI-INFLAMMATORY EFFECT

Animal models

1. **Systemic shock induced by LPS**
2. **Mouse models of neurodegeneration**

- Acute anti-inflammatory effects in the shock systemic model induced by LPS (Plasma cytokines: TNFα and IL-6)
- Subchronic anti-inflammatory effect in the shock systemic model induced by LPS (brain Ho-1 expression and primary lymphocyte inflammatory response)
- Anti-inflammatory effect in mouse models of neurodegeneration (central and peripheral effects).

CURRENT STATUS OF THE DEVELOPMENT

PRECLINICAL DEVELOPMENT: REGULATORY TOXICOLOGY

	Study	Current status
Chemical & Galenic development	**Method validation**	
	Treatment solutions analysis	V
Pharmacodinamics	Receptor binding	
	Receptor binding assay	V
Safety pharmacology	**Core battery**	
	Central nervous system (Irwin test)	Ongoing
	Cardiovascular system studies (hERG)	V
	Telemetry studies in dog	Ongoing
	Respiratory studies in rats	Ongoing
Toxicology	**Repeated doses**	
	DRF in rats (14 days)	V
	MTD in dogs (14 days)	V
	28 day study in rats	V
	28 day study in dogs	V
	Mutagenesis studies	
	Ames test	V
	Mouse lymphoma assay	V
Pharmacokinetics and metabolism	**Method validation**	
	Method validation in rat plasma	V
	Method validation in dog plasma	V
	Metabolism	
	Liver microsomes studies	V
	Plasma binding protein assay	Ongoing
	Toxicokinetics	
	TK in DRF in rats	V
	TK in MTD in dogs	V
	TK in 28 day study in rats	V
	TK in 28 day study in dogs	Ongoing

CURRENT STATUS OF THE DEVELOPMENT

CLINICAL DEVELOPMENT

FIH "First in-human trial of NST0037, a randomised, double-blind, and placebo-controlled, single centre study to evaluate the safety and tolerability of single ascending oral doses in healthy male volunteers"

Objetives and endpoints	
Primary objetive	Tolerability
Primary endpoints	MTD
Secondary objetive	PK NST0037 and its main metabolite profile
Secondary endpoints	Cmax, Tmax, AUC and $t_{1/2}$
Trial design	
Type	Phase I
Design	Randomised, double-blind, placebo-controlled, single centre study.
Medication assignation	3:1

Proof-of-concept

1. In epilepsy
2. In MCI as a disease modifier

Thoughts, Opinions, and Controversies

How Statins Could Be Evaluated Successfully in Clinical Trials for Alzheimer's Disease?

American Journal of Alzheimer's Disease & Other Dementias®
27(3) 151-153

DOI: 10.1177/1533317512442998
http://aja.sagepub.com
SAGE

Javier S. Burgos, PhD[1], Jesús Benavides, PhD[2], Patrice Douillet, MD[3], Javier Velasco, PhD[1], and Fernando Valdivieso, PhD[1]

CURRENT STATUS OF THE DEVELOPMENT

FUTURE LANDMARKS

- ❖To complete regulatory toxicology
- ❖To complete CMC activities
- ❖To complete long-term studies vs simvastatin
- ❖To better characterize the anti-epileptic effect
- ❖To prepare IMPD and IB
- ❖To start FIH
- ❖To find a partner

DIFFERENCIAL FEATURES FACING MARKET

vs SIMVASTATIN

Epilepsy

✓Better anti-epileptic effect than simvastatin

MCI-to-AD

✓Better acute neuroprotective effect than simvastatin

MCI-to-AD

❖Chronic studies vs simvastatin ongoing

vs other drugs

Epilepsy

✓Better anti-epileptic effect than other marketed antiepileptic agents

MCI-to-AD

✓Similar or better capacity to reduce Aβ burden than other drugs in clinical trials, but an improved safety profile

Better PK plasma profile

✓ Completed
❖ Ongoing

DIFFERENCIAL FEATURES FACING MARKET

Selected Drug Candidates in Development For Treating Alzheimer's Disease

Drug Name	Company	Mechanism	Phase
Dimebon (latrepirdine)	Pfizer/Medivation	Anti-beta amyloid	3
Bapineuzumab	Elan/Johnson & Johnson	Anti-beta amyloid monoclonal antibody	3
Semagacestat (LY450139)	Eli Lilly	Gamma-secretase inhibitor	3
Solanezumab (LY2062430)	Eli Lilly	Anti-beta amyloid monoclonal antibody	3
Gammaglobulin IV	Baxter	Passive immunization	3
CERE-110	Ceregene Inc.	Gene therapy to deliver the nerve growth factor gene	2
ACC-001	Elan/Johnson & Johnson	Anti-beta amyloid vaccine	2
PF-4360365	Pfizer	Anti-beta amyloid monoclonal antibody	2
NIC5-15	Humanetics	Insulin sensitization, gamma-secretase inhibitor	2
R3487	Roche	Nicotinic alpha-7 partial agonist	2

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DIFFERENCIAL FEATURES FACING MARKET

Antiepileptic

Anti-inflammatory

Neuroprotective

Hypocholesterolemic

NST0037

Other back-up molecules

Different mechanism of action

Scalable

Safety profile

Advanced status of development

Low cost synthesis

FIH design

IPR PROTECTION

WO2010119161 ("Antiepileptic, hypocholesterolemic and neuroprotective compound")

PRIORITY DATE **16/04/2009.** European Patent Application

PCT EXTENSION **16/04/2010**

ISA **5/11/2010**. Written opinion of the International Searching Authority (ISA)

IPER **26/07/2011.** International Preliminary Report on Patentability

REGIONAL PHASES

Europe, United States of America, Israel, Australia, Canada, India, Mexico, Japan & Brazil

PITFALLS AND RISKS TO BE CONSIDERED

AD indication

Lack of endpoints

Difficulties in the clinical trial design and development

Long-lasting complete development

Epilepsy indication

A number of marketed antiepileptic drugs

The partening opportunities

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❑ **Neuron Biopharma is looking for a partner (a pharmaceutical company or an investment group, etc.) to support the preclinical and clinical development of this promising candidate compound.**

❑ **The degree of involvement of the partner in the development of NST0037 is open to discussion. Profit distribution will depend on the partner's contribution.**

Contact details

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