Targeting the cause of neurodegenerative and autoimmune diseases

June 2019

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GeNeuro's mission

To develop therapies that improve the life of patients with neurodegenerative and autoimmune diseases

- Leveraging the biology of human endogenous retroviruses (HERVs) to stop causal factors associated with these disorders

- The HERV field is a new frontier pioneered by GeNeuro since 2006, based on 15 years of R&D at Institut Mérieux and INSERM

- **Approach validated through results on Multiple Sclerosis disease progression markers in a Phase IIb clinical trial**

Recent data validates GeNeuro's platform approach against pathogenic HERV proteins

- Positive results of temelimab 1 year 270-patient RRMS Phase IIb and its 1 year extension
  - Consistent benefit with temelimab at highest dose on the key markers of neurodegeneration linked to disease progression
  - At two years, first encouraging signs of dose-dependent effects on clinical measures of disease progression
  - Observed effects independent of inflammatory activity of the patients, confirming direct neuroprotective mode of action
  - Results strongly supported by preclinical evidence and mode of action rationale

➢ Clear positioning against **non-active progression**, key unmet medical need in MS

- Successful Phase IIa of temelimab in T1D
- Preclinical development of new anti-pHERV-K monoclonal antibody as treatment option for ALS, in partnership with the NIH
- Wide application potential in other autoimmune and degenerative diseases

First mover in HERV-mediated diseases

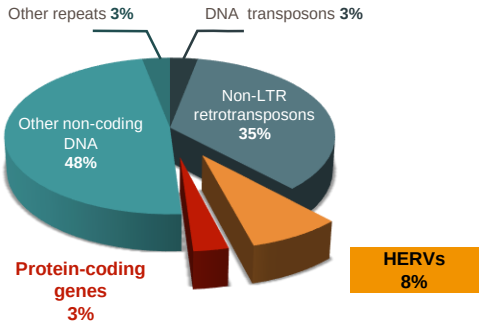
Program	Pre-clinical	Phase I	Phase IIa	Phase IIb	Phase III
1. Temelimab Multiple Sclerosis	Planning next stage developments based on positive neurodegeneration 96-week results				
CHANGE-MS	**270 patients / 50 centers** in the RRMS indication / Completed March 2018				
ANGEL-MS	**219 patients extension of CHANGE-MS**/ Completed March 2019				
3. Temelimab Type 1 Diabetes	Safety & signal finding Phase IIa				
	Launched April 2017 / 6-month data Sept. 2018, full 12-month data 2Q2019				
4. Temelimab CIDP	ODD granted by the US FDA				
	Planning discussions with FDA to design a proof-of-concept study				
5. Anti-HERV-K ALS	**R&D Agreement with NIH, IND submission planned by mid-2020**				
6. New anti HERV-W Ab Inflammatory Psychosis	Research collaborations with Academic labs				

Human Endogenous Retroviruses (HERVs)

Ancestral retroviral genomic (DNA) insertions

HERV elements are latent in human genome

- Represent approximately 8% of total human genome
- Genetic transposition leads to variable copy number, with non-ubiquitous copies in individuals
- HERVs are normally latent but may be de-repressed and transcribed to produce viral proteins



Missing link between viral infections and poorly understood autoimmune / neurodegenerative diseases

- Strong epidemiology data associates environmental viruses with diseases such as MS and T1D
- Environmental viruses do not appear to play a direct role in disease development
- They can activate HERV genes upon infection of permissive cells
- Pathogenic HERV proteins have been suggested as potential causal factors in autoimmune / neurodegenerative diseases

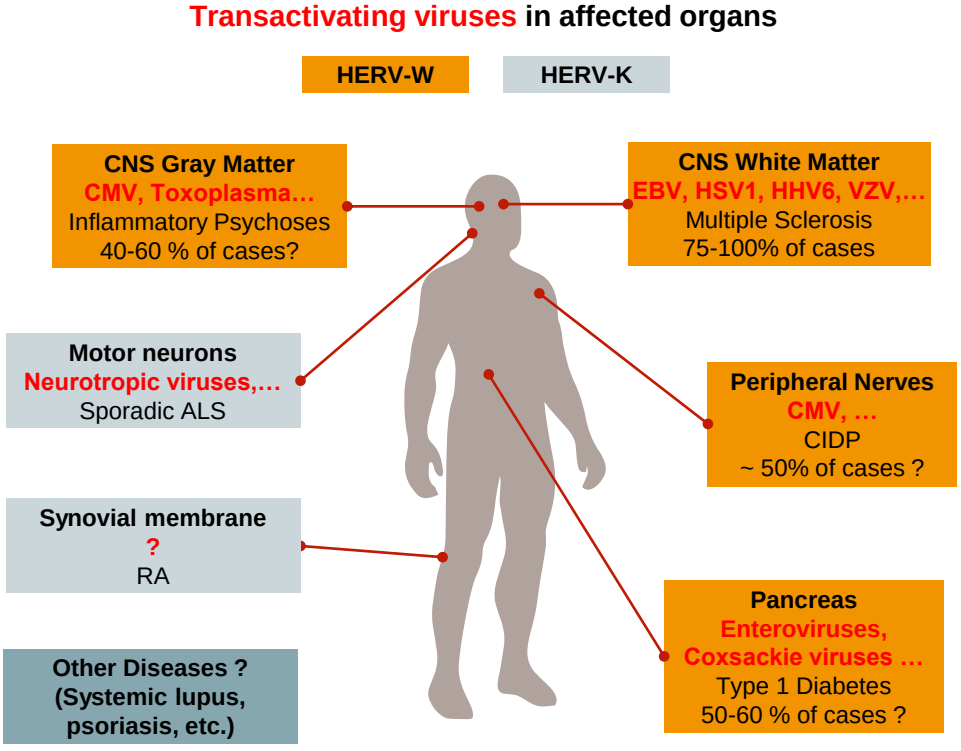
nature medicine

The enemy within: dormant retroviruses awaken
Engel & Hiebert, Nature Medicine, 2010

Sources: Regulatory evolution of innate immunity through co-option of endogenous retroviruses; Science, Vol. 351, Issue 6277
Discovery of unfixed endogenous retrovirus insertions in diverse human populations. Proc Natl Acad Sci U S A. 2016
Human Endogenous Retrovirus Type W Envelope Protein Inhibits Oligodendroglial Precursor Cell Differentiation; Ann Neurol. 2013;74(5)A

Viruses triggering HERV Proteins and link to disease

Examples of pHERV Env mediated diseases



- Pathogenic HERV proteins found at high levels in affected organs
- Pathogenicity is generally mediated by (abnormally expressed) viral envelope proteins – pHERV Env W, K...
- pHERV Env directed toxicities found in:
  - Microglia
  - OPCs
  - Pancreatic beta islet cells
  - Motor Neurons
  - Schwan cells
  - Others…

Broad and strong IP supporting first mover advantage

- Mérieux Group & GeNeuro worked for more than 25 years in the HERV field
- 16 families of patents in HERV-W*, including the following 3 broad categories:
- **Key granted patents on temelimab filed from 2008 to 2014**
  Strong IP development strategy to continue protecting temelimab beyond 2034 (2039 w. SPC)

SEP 16 family	**TLR4 family**	**MSRV* ligand family**
Background including sequences	Antibody strategy against target	Product patents & disease areas

Existing IP portfolio & constant efforts to protect new discoveries place GeNeuro in a strong competitive position

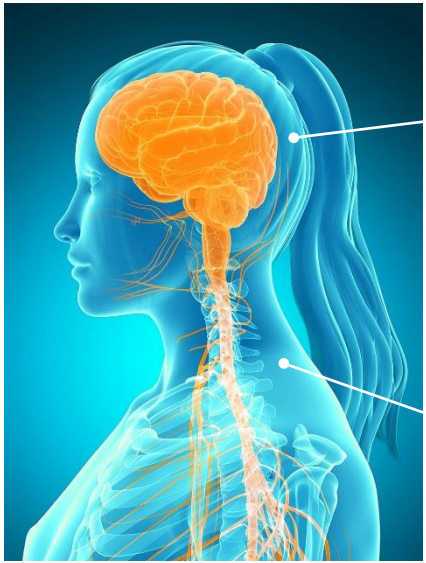
- **New anti pHERV-K patent, co-owned with and in-licensed from NIH**

** previous name of pHERV-W Env*

Temelimab mode of action in MS

2.5 million MS patients worldwide
$21.8 bn market in 2018

MS is a life-long inflammatory and degenerative disorder of the central nervous system

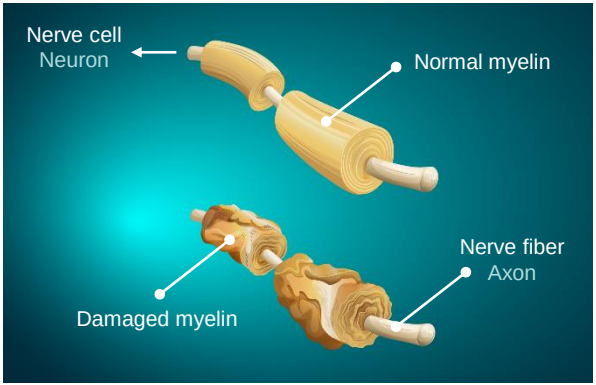


Brain impairment

Vision, cognition
motor coordination,
equilibrium

Spinal cord impairment

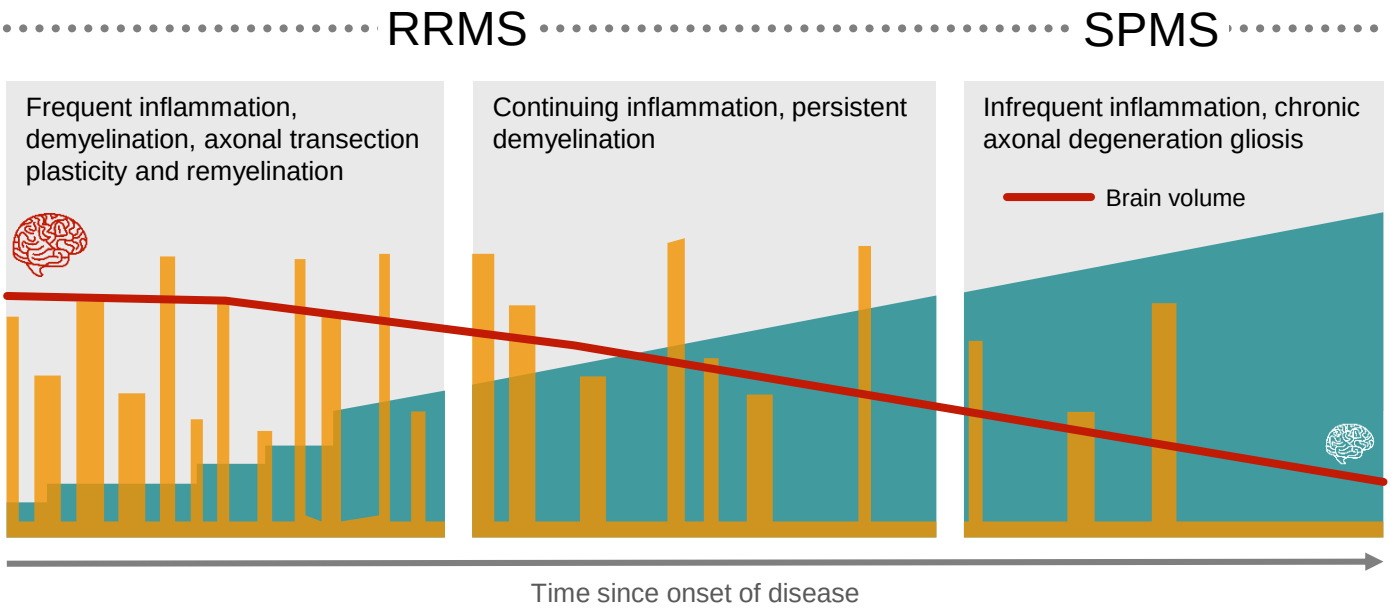
Walking, strength,
sensation, sexuality,
bowel / bladder control



- Disease onset mainly occurs in young adults
- Female to male ratio is 2:1
- Mean prevalence about 1/1000

Source: Inserm/Disc : F. Koulikoff.

From the outset of disease, Multiple Sclerosis is marked by neuroinflammation and axonal loss/brain atrophy



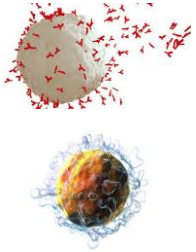
Inflammation	Inflammation mediated by adaptive immunity (B and T lymphocytes)
Axonal loss	Neuronal damage mediated by innate immunity (activated microglia) and accelerated by hampered remyelination (oligodendrocyte precursor cells)

Adapted from Compston et al., The Lancet 2002 - RRMS: Relapsing-Remitting MS; SPMS: Secondary Progressive MS

Known drivers of multiple sclerosis and existing therapeutic agents

Adaptive Immunity

T- and B-cells are selectively recruited to the CNS

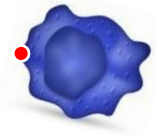


Target of most DMTs

- α-CD20s mAbs
- $S_1P_{1/n}$ agonists
- α-integrin mAb
- etc.

Innate Immunity

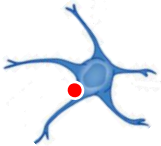
CNS resident Microglia



No approved drugs

Repair

Dysfunctional
Oligodendrocyte Precursor Cells (OPCs)

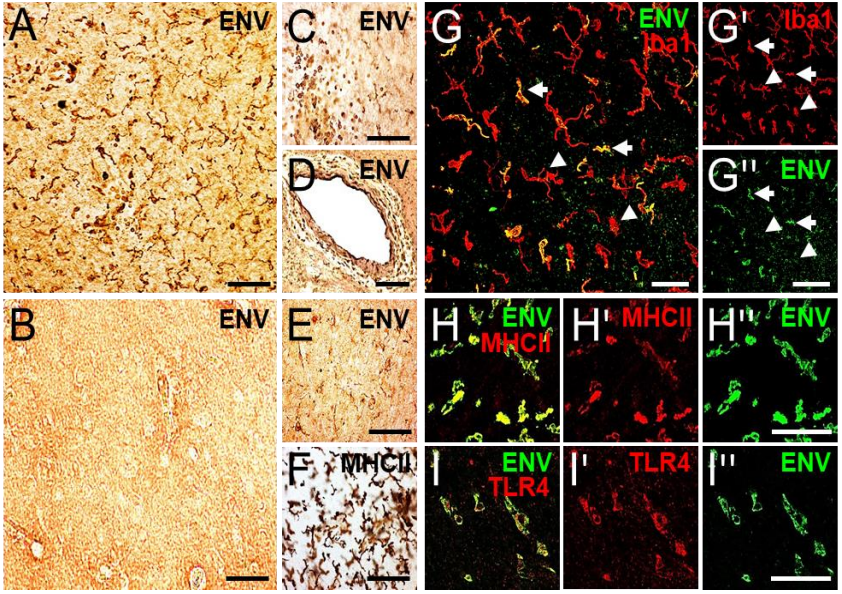


No approved drugs

Consistent presence of pathogenic HERV-W Envelope protein (pHERV-W Env) in the brains of MS patients

Highly expressed in active MS lesions

- Consistently found in MS brains
- Expression levels correlate with lesion activity
- Present from earliest to latest stages of disease
- Env is predominantly present in microglial/monocytic cells in the MS brain belonging to the innate immune system



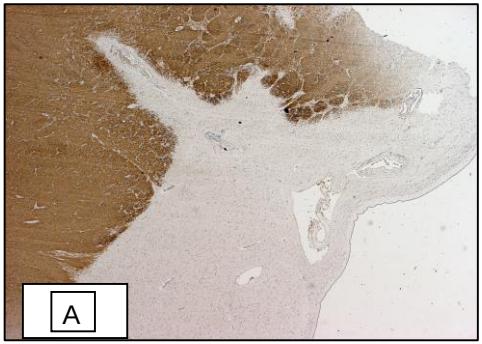
pHERV-W Env positive microglial/monocytic cells in MS lesions
Kremer et al., under revision

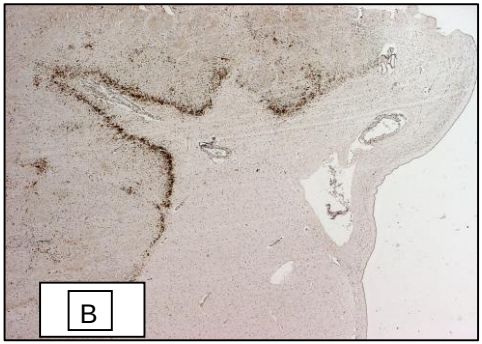
Sources: Perron et al., MS Journal, 2012; Van Horssen et al.,MS & Related Disorders 2016; Rolland et al., J Immunol, 2006; Antony et al., Nat NeuroSci, 2004; Kremer et al., Ann. Neurol, 2013; Perron et al., PLOS One, 2013; Madeira et al., J Neuroimmunol 2016

pHERV-W Env protein is expressed in progressive MS lesions

- In progressive plaques, pHERV-W Env is expressed in the demyelinating border composed of activated microglia

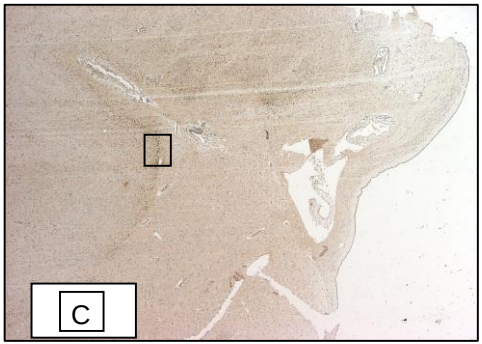
A - Chronic plaque with microglial line (myelin in brown)

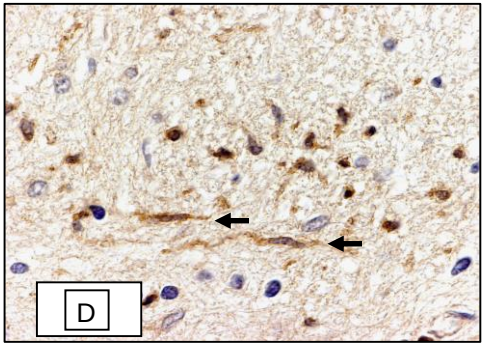




B - The line of microglia is highly activated (HLA-DR+++).

C – pHERV-W Env is expressed in the microglial line only

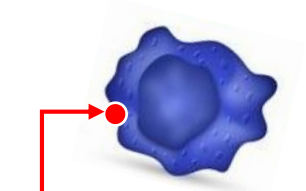




D - Activated and migrating microglial cells are strongly positive for pHERV-W Env

Sources: Perron et al., MS Journal, 2012 & Van Horssen et al.,MS & Related Disorders 2016 & Rolland et al., J Immunol, 2006 & Antony et al., Nat NeuroSci, 2004 & Kremer et al., Ann. Neurol, 2013 & Perron et al., PLOS One, 2013, Madeira et al., J Neuroimmunol 2016

pHERV-W Env acts on key cells associated with MS disease progression: Microglia and OPCs



TLR4⁺ (●)
Microglia

pHERV-W Env

- induces an agressive phenotype (M1) in TLR4⁺ microglial cells
- activates microglia to associate themselves with myelinated axons
- decreases microglial expression of regenerative factors

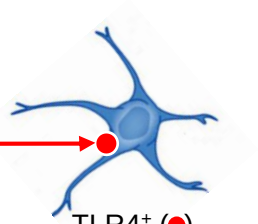
→ **fuels microglial-dependent neurodegeneration in MS**

pHERV-W Env

pHERV-W Env

- induces release of cytokines & activates NO synthase
- reduces myelin protein expression
- significantly reduces OPC differentiation capacity

→ **drives OPC mediated remyelination failure**



TLR4⁺ (●)
Oligodendrocyte Precursor Cell (OPCs)

Sources: Kremer et al., Ann Neurol 2013; Antony et al., Nat NeuroSci 2004; Madeira et al, JNeuroImmunol 2016; Rolland et al., J Immunol 2006; Kremer et al. presentation at the 2018 Charcot Conference

pHERV-W Env fuels microglial cell mediated neurodegeneration in MS

Microglia activation yields agressive phenotype

pHERV-W Env activates microglia in neuron / oligodendrocyte co-cultures, leading to axonal injury due to increased TNFα.

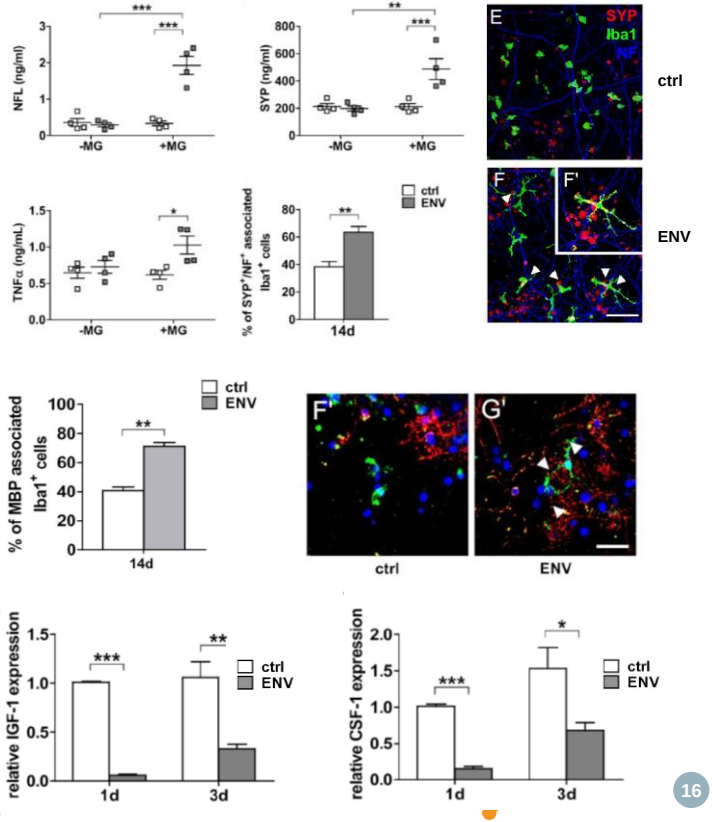
- Release of axonal neurofilament light chain (NFL)
- Release of synaptophysin (SYP)

Microglia are directed towards myelinated axons

In neuron / oligodendrocyte / microglia co-cultures pHERV-W Env induces microglia to associate themselves with axonal structures.

Regenerative factors in microglia decreased

Stimulation of microglia with pHERV-W ENV leads to significant decrease of regenerative genes transcription (IGF-1, CSF-1, FGF-2) in microglia.

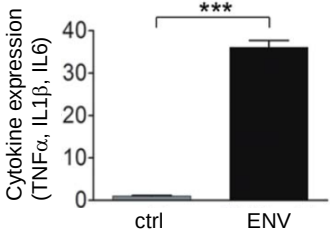


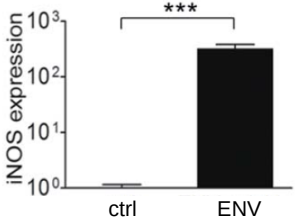
Source: Kremer, Küry et al. presentation at Charcot Conference, Nov 2018

pHERV-W Env drives OPC mediated remyelination failure

OPCs express increased levels of cytokines & iNOS

pHERV-W Env stimulation of rOPCs *in vitro* leads to a strong induction of iNOS expression. Proinflammatory cytokines such as TNFα, interleukin (IL)-1β, and IL-6 are highly upregulated upon stimulation with pHERV-W Env.

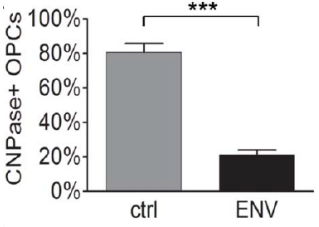


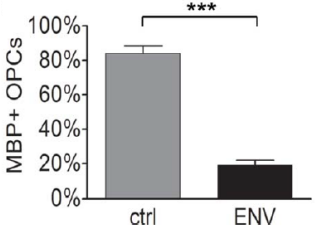


OPC differentiation capacity is significantly reduced

pHERV-W Env markedly decreases number of OPCs expressing early (E) and late (L) markers of myelin:

- 2',3'-cyclic nucleotide 3'-phosphodiesterase, CNPase, (E)
- Myelin basic protein, MBP, (L)

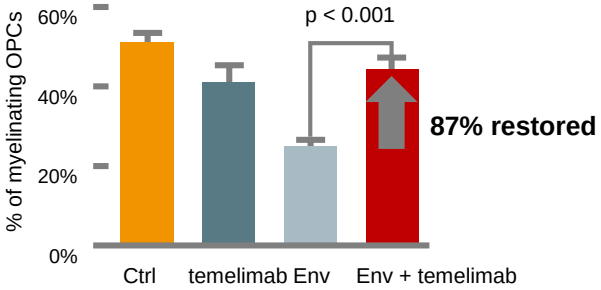




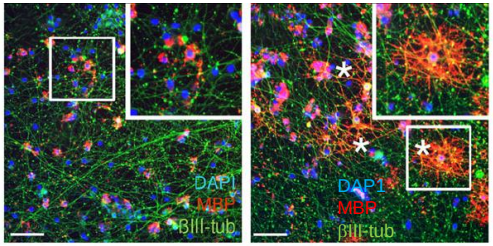
Source: Kremer et al., Ann Neurol 2013

Temelimab (GNbAC1) rescues myelin expression by blocking Env-induced nitrosative stress in OPCs

- Recombinant, humanized IgG4-κ mAb
- PK approx. dose linear, Half-life ≈ 1 month
- Binds with high affinity to pHERV-W Env (K_d = 2.2 nM)
- Blocks pHERV-W Env activation of TLR4
- Rescues MBP* expression in OPCs



In vitro myelinating co-cultures displaying the **temelimab** mediated rescue of myelinated segments (MBP in red)



*MBP: Myelin Basic Protein; marker of OPC maturation

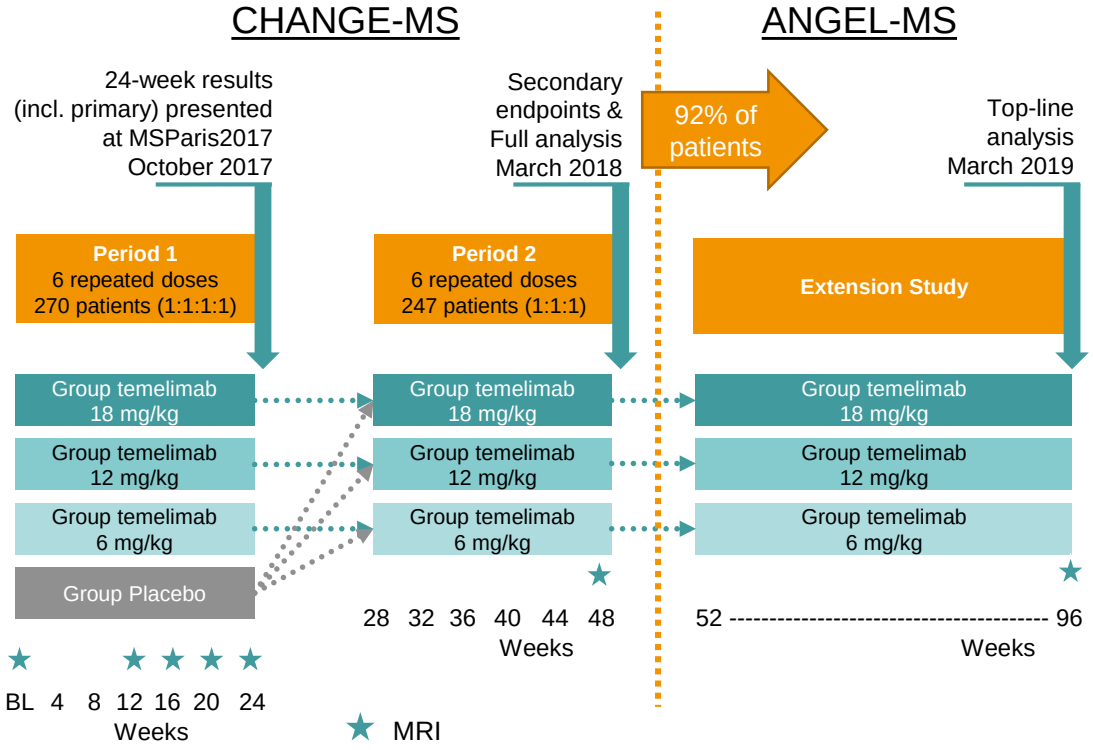
Source: Kremer et al. Mult Scler. 2015, Göttle et al. Glia 2018, Data presented at MSParis2017 - Late Breaking News

Temelimab clinical results in MS

Phase IIb trial (CHANGE-MS followed by ANGEL-MS)

Efficacy in RRMS patients at 6 months, 1 year and 2 years

- International, randomized, double-blind, placebo-controlled Phase 2b study in RRMS patients + extension
- Primary Endpoint: Cumulative # Gd+ lesions on brain MRI scans at weeks 12-24
- After 24 weeks, the control group is composed of patients originally randomized to placebo.
- Remyelination and neuroprotection endpoints at 48 weeks and at week 96 in extension study



Administration: IMP IV every 4 weeks

ANGEL-MS: extension study to CHANGE-MS assessing safety & efficacy of temelimab in RRMS patients

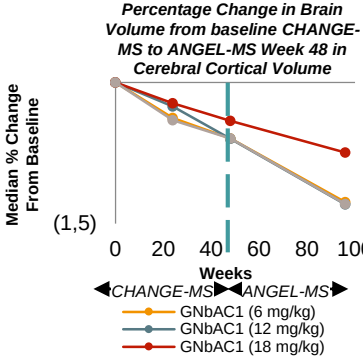
- 219 patients from CHANGE-MS entered ANGEL-MS (92% of completers)
  - Early termination was a result of Servier's decision to opt-out
  - 154 patients (70%) completed 96 weeks or more across the combined studies
  - Approximately 90% of patients completed at least 86 weeks
- All patients remained on active therapy; patients, investigators and MRI reading center remained blinded to dose/original randomization group
- Delays in study start-up led to dose interruptions between the trials
  - > 80% missed ≥ 1 dose; ≈ 50% missed ≥ 2 doses and ≈ 20% missed ≥ 3 doses
- Analysis strategy:
  - As per SAP, original randomization groups: 18, 12 and 6mg/kg & Control Group (defined as patients originally randomized to placebo in CHANGE-MS, and re-randomized to active treatment after 6 months)
  - Several sensitivity analyses performed:
    - (1) by dose groups (placebo patients placed into the active dose group they were re-randomized to)
    - (2) by exposure (separating quartiles by total exposure to temelimab, irrespective of body weight);
    - (3) separating 18mg/kg against all other treatments
  - No adjustments were performed for multiple testing

CHANGE-MS and ANGEL-MS 48-week results position temelimab's against disease progression in MS

- **No clinically relevant benefit on MRI markers of neuroinflammation**
  - Primary endpoint on the reduction of number of Gd+ lesions at Week 24 not met
  - All groups substantially improved from Week 24 to Week 48
  - No significant differences across groups
- **Consistent benefit with temelimab at highest dose on key markers of neurodegeneration, linked to disease progression**
  - Reduction of Brain Atrophy (thalamus, cerebral cortex, deep gray matter and whole brain)
  - Reduction in T1 Black Holes (marker of permanent tissue damage)
  - Benefit seen on Magnetization Transfer Ratio (MTR - measure of remyelination)
- **Temelimab's effect is independent from the inflammatory activity experienced by the patients during the study**
- **First encouraging signals of neuroprotection translating into clinical benefits at 96 weeks**
- **Continued excellent safety and tolerability**
  - Opens the door for possible increase in dose, and/or
  - Combination with powerful anti-inflammatory agents

Clinical data show positive effects of temelimab

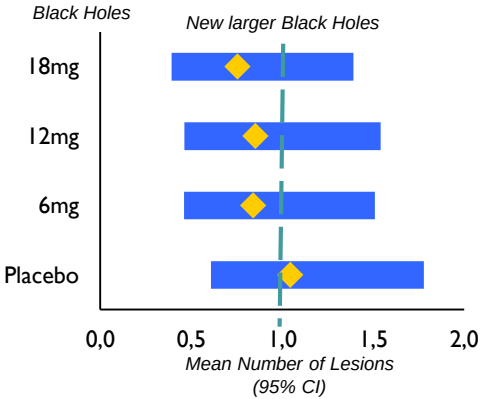
1 Evolution of Cortical Atrophy over 96 weeks



Group	Median % reduction at week 48 in ANGEL-MS	Relative reduction of atrophy
Control	(1.29)	42%
6mg/kg	(1.27)	41%
18mg/kg	(0.75)	

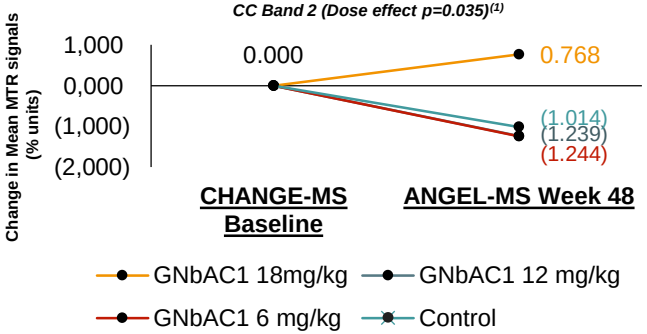
Dose effect p=0.058[1]

3 Reduction of Black Holes at week 48 (not computed at week 96 for technical reasons)



Median reduction between 18mg/kg group and control group in new larger T1 Black Holes[3] *=* ***63%*** *(p=0.014)*

2 Evolution of Cortical MTR[2] signal over 96 weeks

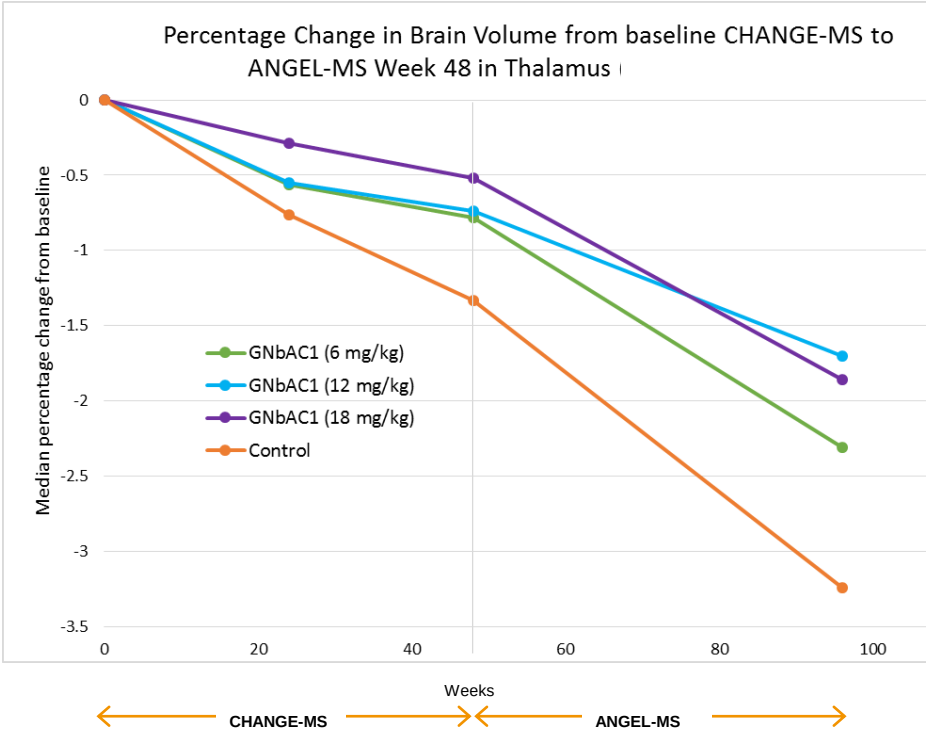


4 Very well tolerated drug

# of Patients (%)	18 mg/kg (N=77)	12 mg/kg (N=68)	6 mg/kg (N=74)
Adverse Events (AEs)	34 (44.2%)	32 (47.1%)	33 (44.6%)
Serious Adverse Events (SAEs)	5 (6.5%)	1 (1.5%)	6 (8.1%)
Serious Related AEs	3 (3.9%)	0	0
AEs Leading to Study Discontinuation	2 (2.6%)	1 (1.5%)	1 (1.4%)
Fatality[4]	1 (1.3%)	0	0

(1) Dose effect analyzed by linear regression, SAS analysis proc GLM; (2) ***MTR*** = Magnetization transfer ratio; (3) T1 hypointense lesion ≥ 14mm3 volume;
(4) Patient had previously voluntarily exited the study; the Investigator considered the event as unrelated.

Continued reduction Thalamic atrophy
Original CHANGE-MS Groups



CHANGE-MS

Group	Median % reduction at week 48	Relative reduction of atrophy
Control	-1.27	
18mg/kg	-0.36	**72%**

Dose effect* p=0.014

ANGEL-MS

Group	Median % reduction at week 48	Relative reduction of atrophy
Control	-3.24	**43%**
6mg/kg	-2.31	**19%**
12mg/kg	-1.70	**-9%**
18mg/kg	-1.86	

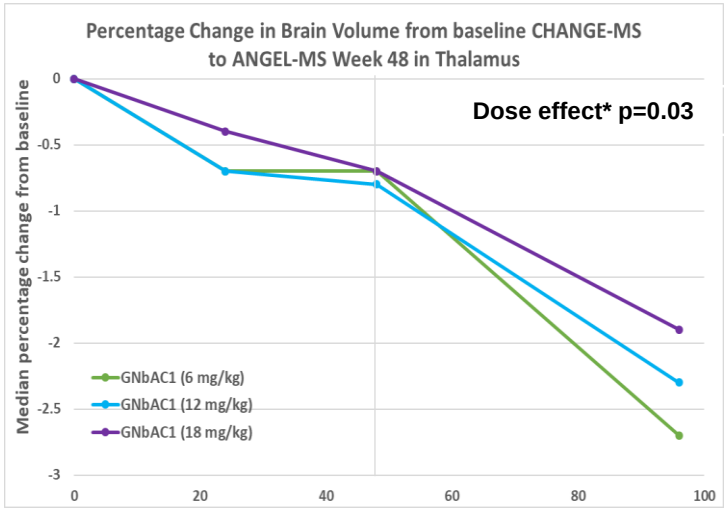
Dose effect* p=0.038

* Dose-effect analyzed by linear regression model

Continued reduction Thalamic atrophy

Sensitivity analysis by Dose and by Exposure

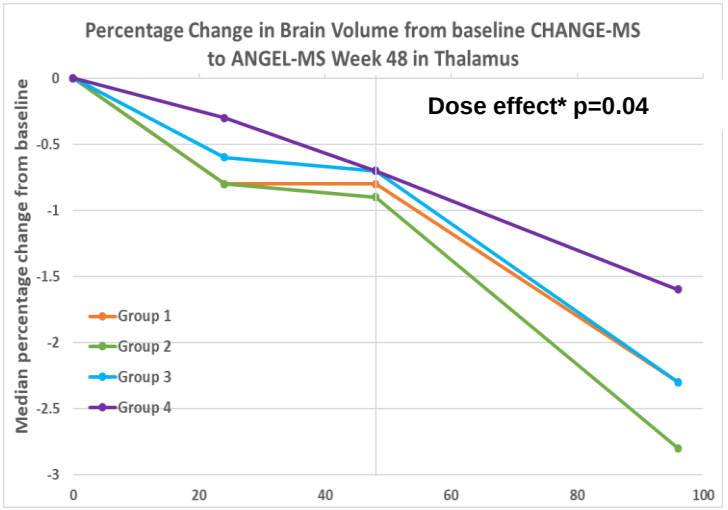
BY DOSE



Group	Median % reduction at week 48 in ANGEL-MS	Relative reduction of atrophy
6mg/kg	-2.7	
12mg/kg	-2.3	**17%**
18mg/kg	-1.9	**30%**

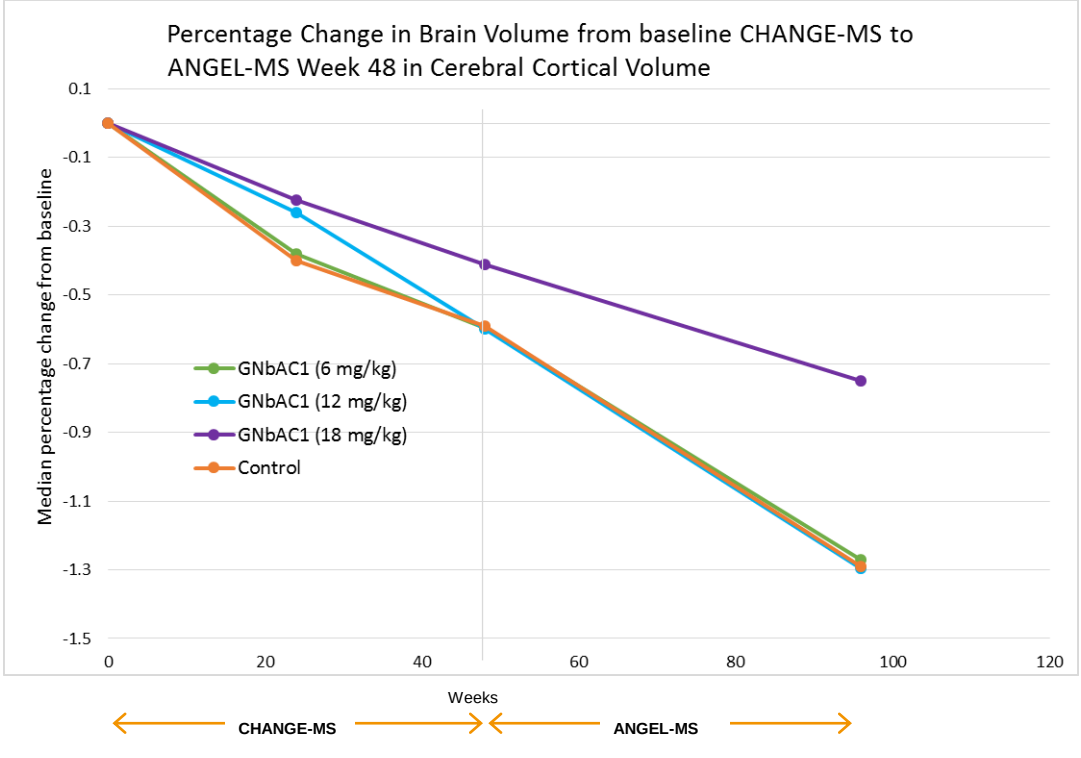
* Dose-effect analyzed by linear regression model

BY EXPOSURE



Group	Median % reduction at week 48 in ANGEL-MS	Relative reduction of atrophy
G1 MIN	-2.3	
G4 MAX	-1.6	**30%**

Continued reduction of Cortex atrophy
Original CHANGE-MS Groups



CHANGE-MS

Group	Median % reduction at week 48	Relative reduction of atrophy
Control	-0.59	
18mg/kg	-0.41	**31%**

Dose effect* p=0.045

ANGEL-MS

Group	Median % reduction at week 48	Relative reduction of atrophy
Control	-1.29	**42%**
6mg/kg	-1.27	**41%**
12mg/kg	-1.29	**42%**
18mg/kg	-0.75	

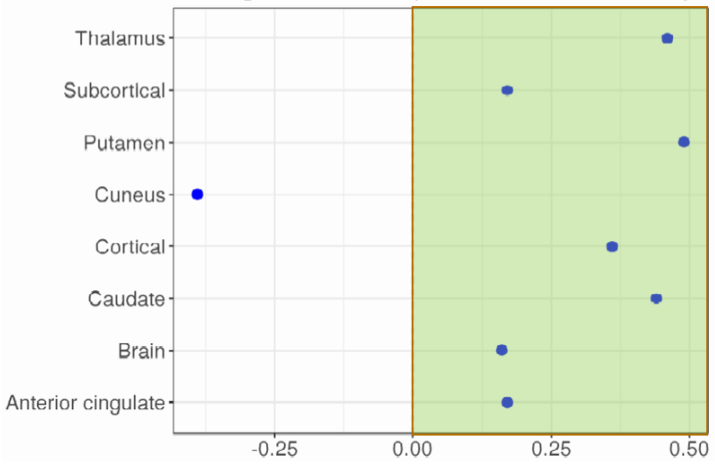
Dose effect* p=0.058

* Dose-effect analyzed by linear regression model

June 2019

Consistent benefit with temelimab seen in non-active population is a key asset

Median change in volume in non-active population* in CHANGE-MS 18mg/kg versus Control Group



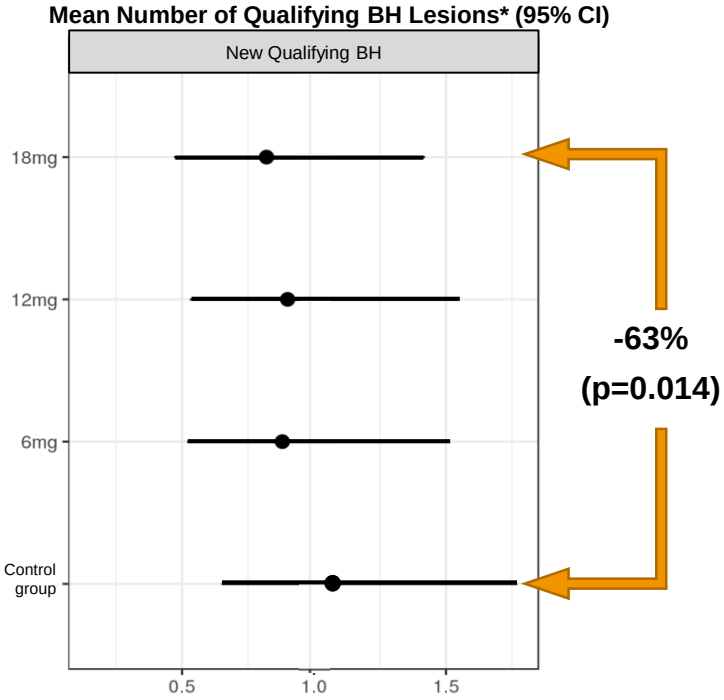
* defined as patients without Gd+ activity at baseline

- Effects of temelimab on OPCs and microglia are not due to immune modulation
- Suggests temelimab monotherapy could effectively target neurodegeneration and promote regeneration in non-active populations
- Suggests temelimab as adjunct to highly-effective DMTs for all forms of active MS

Source: H.P. Hartung et al, ECTRIMS 2018 Presentation

Reduction in the number and volume of new T1 hypointense lesions (Black Holes) through CHANGE-MS and ANGEL-MS

CHANGE-MS Week 48



* T1 hypointense lesion ≥ 14mm^3 volume

ANGEL-MS Week 96

Group	Median percent increase in T1 hypointense lesion volume**
18mg/kg	8.7%
12mg/kg	9.2%
6mg/kg	14.5%
Control Group	21.3%

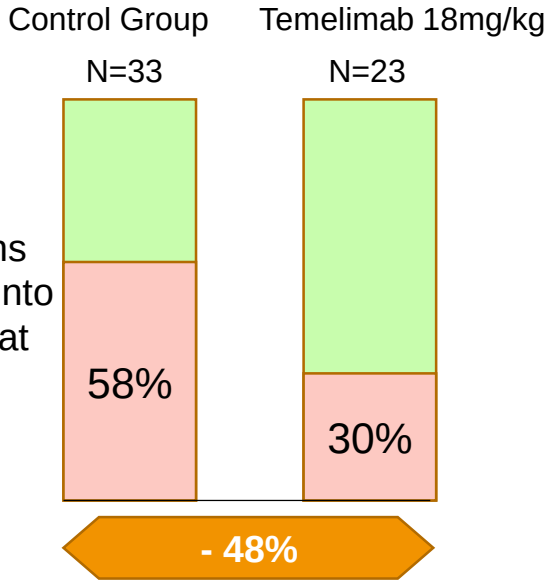
-59%
(p=0.12)

**The set-up of ANGEL-MS did not allow to differentiate acute and chronic T1-hypointense lesions, therefore data not directly comparable to CHANGE-MS measure of chronic lesions

Reduction in risk of lesions at baseline transforming into new T1Black Holes at CHANGE-MS Week 48

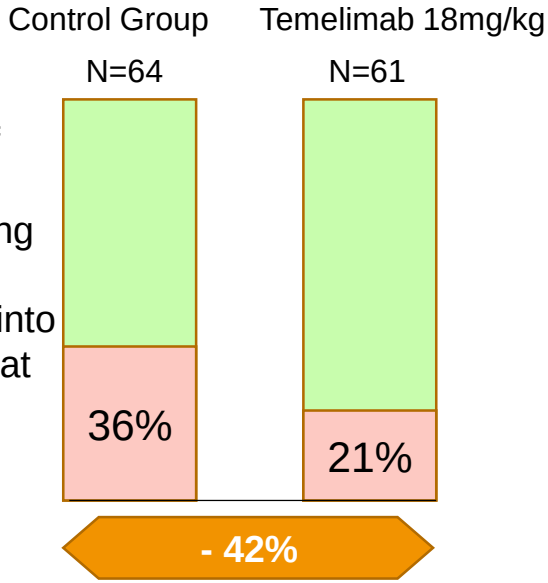
Proportion of patients with T1Gd+ lesions at baseline

Proportion of patients with T1Gd+ lesions transformed into new T1 BHs at week 48



Proportion of patients with non-enhancing T2 lesions at baseline

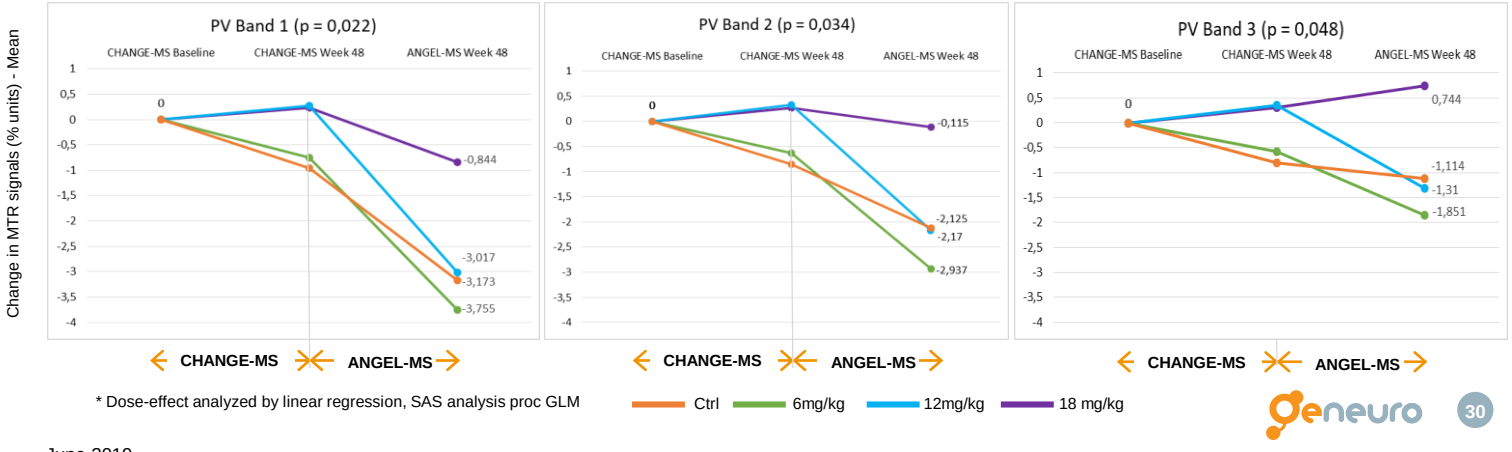
Proportion of patients with non-enhancing T2 lesions transformed into new T1 BHs at week 48



Temelimab preserves myelin integrity over 96 weeks

Normal Appearing White Matter - Original CHANGE-MS Groups

		WEEK 48 ANGEL-MS							
Change in MTR signal from CHANGE-MS BL (% units)		**18 mg**	**12 mg**	**6 mg**	**Control**	**Gain 18 vs 12**	**Gain 18 vs 6**	**Gain 18 vs Ctrl**	**Trend p***
NAWM Band 1	mean	-0.84	-3.02	-3.76	-3.17	2.18	2.91	2.33	0.022
	median	-1.83	-3.55	-3.39	-3.52	1.72	1.56	1.69	
NAWM Band 2	mean	-0.12	-2.17	-2.94	-2.13	2.05	2.82	2.01	0.034
	median	-0.99	-2.70	-2.16	-2.65	1.71	1.17	1.66	
NAWM Band 3	mean	0.74	-1.31	-1.85	-1.11	2.05	2.60	1.86	0.048
	median	-0.32	-1.42	-0.86	-1.35	1.10	0.54	1.03	

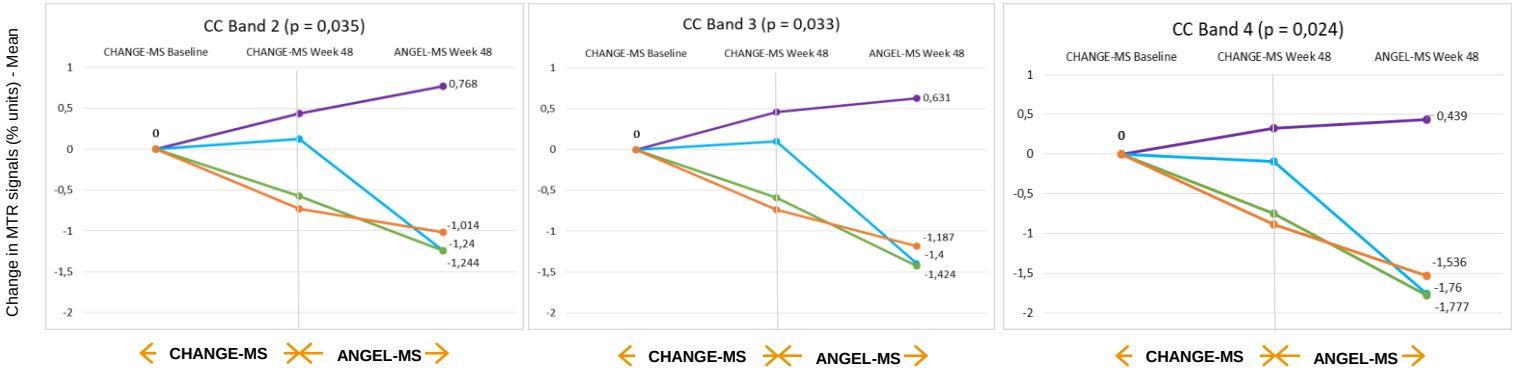


* Dose-effect analyzed by linear regression, SAS analysis proc GLM

Temelimab preserves myelin integrity over 96 weeks

Cerebral Cortex - Original CHANGE-MS Groups

		WEEK 48 ANGEL-MS							
Change in MTR signal from CHANGE-MS BL (% units)		**18 mg**	**12 mg**	**6 mg**	**Control**	**Gain 18 vs 12**	**Gain 18 vs 6**	**Gain 18 vs Ctrl**	**Trend p***
CC Band 2	mean	0.77	-1.24	-1.24	-1.01	2.01	2.01	1.78	0.035
	median	0.00	-0.89	-0.73	-0.96	0.89	0.73	0.96	
CC Band 3	mean	0.63	-1.40	-1.42	-1.19	2.03	2.06	1.82	0.033
	median	-0.01	-0.97	-1.07	-1.20	0.96	1.06	1.19	
CC Band 4	mean	0.44	-1.76	-1.78	-1.54	2.20	2.22	1.98	0.024
	median	0.13	-1.11	-1.12	-1.41	1.24	1.25	1.54	



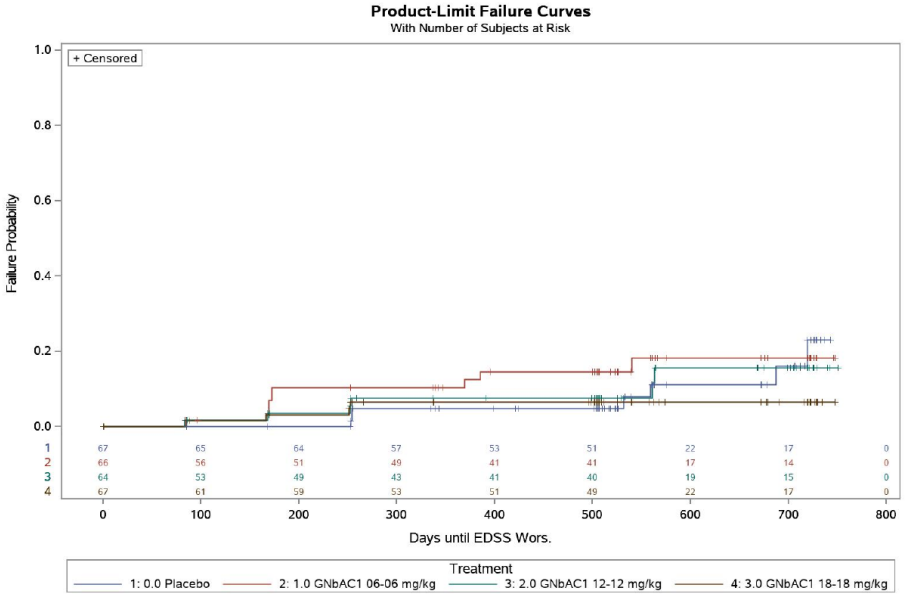
* Dose-effect analyzed by linear regression, SAS analysis proc GLM

Lower probability for confirmed disability progression observed - Original CHANGE-MS Groups

	18 mg/kg	12 mg/kg	6 mg/kg	Control
% of patients with 12-week confirmed worsening in neurological disability from CHANGE-MS baseline to week 48 ANGEL-MS	3.8	4.8	8.3	9.1

Lower probability of 12-week confirmed disability progression in the 18 mg/kg group, but not reaching statistical significance:

- Survival Wilcoxon overall test p=0.34
- Log-rank overall test p=0.45
- Hazard ratio 18mg/kg vs control = 0.50, pairwise comparison p=0.27



Encouraging signs of clinical benefit on Timed 25-Foot Walk

Original CHANGE-MS groups and Sensitivity analyses

Timed 25-foot walk – Original CHANGE-MS Groups	18 mg/kg	12 mg/kg	6 mg/kg	Control	P-value**
Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*	2.4	23.1	13.3	10.2	0.03

Timed 25-foot walk – By Dose Groups	18 mg/kg	12 mg/kg	6 mg/kg	P-Value**
Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*	3.6	16.9	15.0	0.04

Timed 25-foot walk – By 18 vs Others	18 mg/kg	Others	P-value**
Percentage of patients with worsening ≥ 20% in the Timed 25-Foot Walk Test compared to CHANGE-MS Baseline*	2.4	15.0	0.03

*Fifteen outliers (patients with extreme walking disability) removed from analysis – excluded patients distributed equally across treatment groups

**Fisher exact test

Temelimab was safe and well tolerated over two years

Number of patients (%)	18 mg/kg (N=77)	12 mg/kg (N=68)	6 mg/kg (N=74)
Adverse Events (AEs)	34 (44.2%)	32 (47.1%)	33 (44.6%)
Serious adverse events (SAEs)	5 (6.5%)	1 (1.5%)	6 (8.1%)
Serious related AEs	3 (3.9%)	0	0
AEs leading to study discontinuation	2 (2.6%)	1 (1.5%)	1 (1.4%)
Fatality*	1 (1.3%)	0	0

* Patient had previously voluntarily exited the study; the Investigator considered the event as unrelated.

June 2019

Efficacy findings are supported by preclinical data

Clinical observations

- **Reduction of Brain Atrophy**
- **Reduction in new T1 Black Holes**
- **Benefit on Magnetization Transfer Ratio**
- **Effects on markers associated with disease progression not due to immune modulation**
- **Promising a novel treatment option against neurodegeneration in all forms of MS**

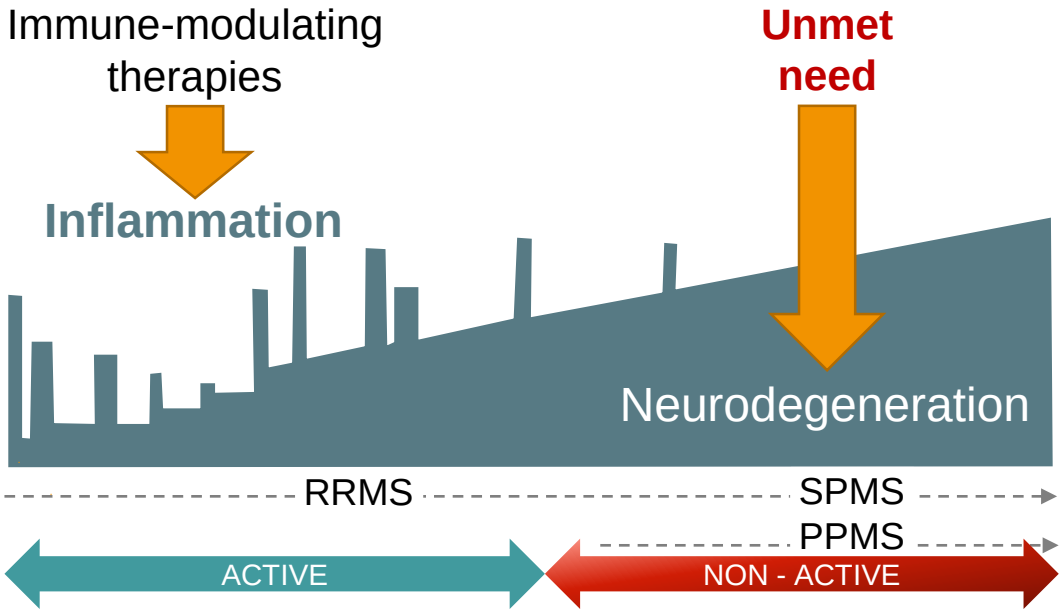
Supporting pre-clinical data

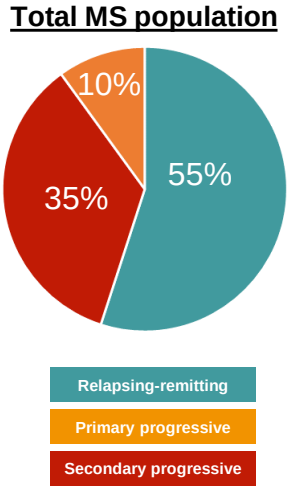
- **Neurodegeneration reduced** by
  - directly **acting on** proinflammatory **microglia,** the key immune cells in PMS, responsible for lesion growth and exacerbation
- **Neuroregeneration enabled** by
  - rescuing the negative impact of pHERV-W Env on **OPC** maturation - the key cells in the remyelination process.
- **No direct effect on T/B lymphocytes** and thereby not compromising adaptive immunity
- **Excellent preclinical safety package** based on a stabilized IgG4 backbone, low immunogenicity and a linear PK at all doses

Sources: Kremer et al., Ann Neurol 2013; Kremer et al., Mult Scler J 2015; *Luo et al., Neuropsychiatr Dis Treat 2017; Göttle et al. Glia 2018; Küry et al., Trends Mol Med; Kremer et al. presentation at the 2018 Charcot Conference

Temelimab positioning in MS

Objective: develop a new treatment effective against non-active disease progression

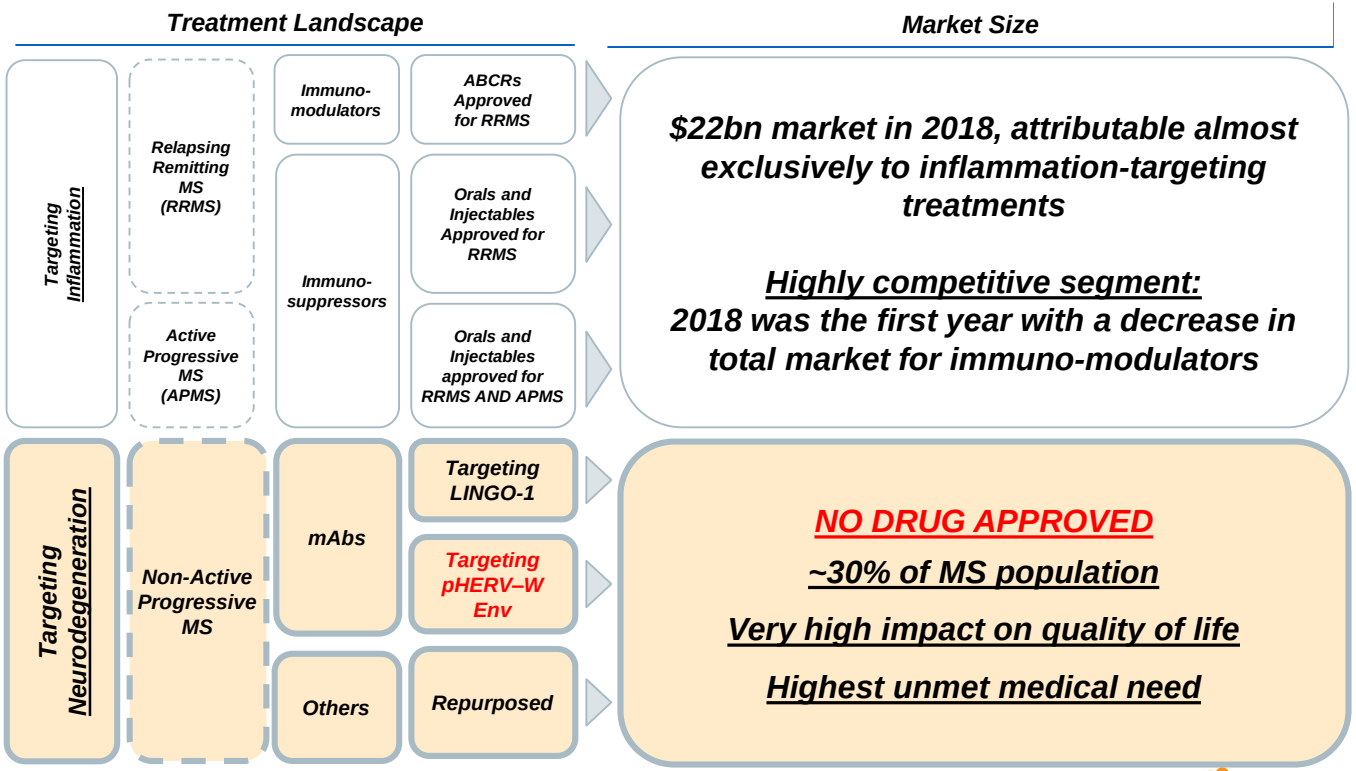




Distinction recently clarified by the FDA

"Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS. Later, many patients with SPMS stop experiencing new relapses, but disability continues to progress, a phase called non-active SPMS."
FDA Press release on Siponimod approval, March 26, 2019

GeNeuro Offers a Unique, Unencumbered Opportunity in MS…



Sources: EvaluatePharma, Annual reports of companies active in MS

June 2019

Drugs in development that specifically target neurodegeneration

Drug	Company	Pharmacology	Proposed Mode of Action	Dev. Stage
Opicinumab	Biogen	Monoclonal antibody IgG1 neutralizing LINGO-1 protein	Favoring oligodendrocyte differentiation and remyelination	Ongoing Phase IIb
Biotin	MedDay	Vitamin B8/H given at high dose (300mg/day)	Increasing energy supply (ATP, fatty acid) to oligodendrocytes favoring myelin production	Ongoing Phase 3
Ibudilast	MediciNova	Anti-inflammatory drug, approved in Japan for asthma since 1989	Inhibition of macrophage migration, decrease of TNFα, enhancing survival and maturation of oligodendrocytes	Completed Phase IIb
Masitinib	AB Science	Selective tyrosine kinase inhibitor developed in neurology, inflammatory diseases and oncology	Inhibiting mast cell degranulation to avoid proteolysis, secretion of vasoamines and release of pro-inflammatory chemoattractants	Phase III ongoing
Temelimab	GeNeuro	Monoclonal antibody IgG4 neutralizing pHERV-W-Env, associated to MS as a causal factor	Enhancing remyelination and reducing damage by promoting OPC maturation and blocking microglial activation	Completed Phase IIb

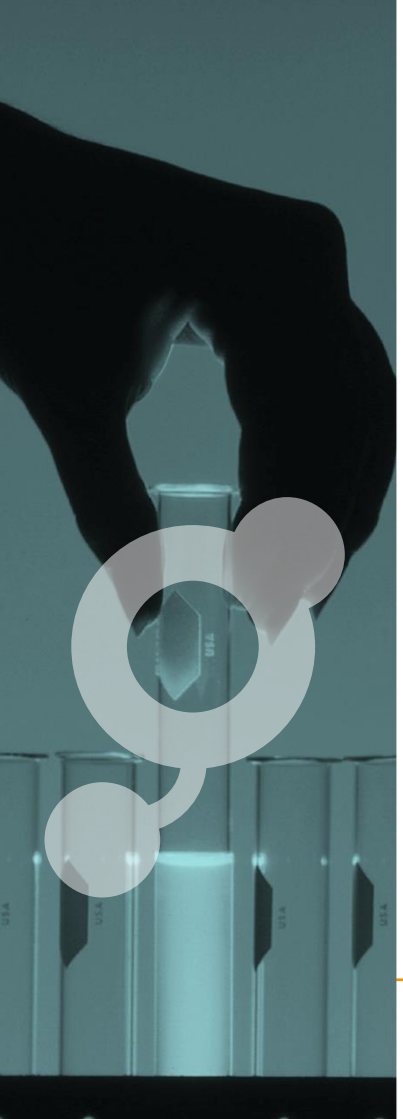
Sources: Mellion et al., Neurology 2017 ; Kremer et al., MSJ 2018 In print; Green et al., Lancet 2017; Company web sites

The ANGEL-MS results further support development of temelimab to prevent disease progression in MS

- **Disease progression remains the key unmet medical need in MS**
  - "The greatest remaining challenge for multiple sclerosis is the development of treatments incorporating neuroprotection and remyelination to treat and ultimately prevent the disabling, progressive forms of the condition."
    Prof. Alan J Thompson, Lancet 2018; 391: 1622–36

- **Development plan**
  - As **monotherapy,** in non-active Progressive MS patients, where the unmet medical need is the highest
  - In **combination** with an existing anti-inflammatory drug, to slow-down / prevent progression on treated Relapsing MS patients (rendered "non-active" by their inflammatory treatment), an area in which current treatments have modest impact

- **GeNeuro is fully committed to further develop temelimab in MS**



Part 2

Temelimab in T1D

Overview of Type 1 Diabetes

- Type 1 Diabetes is a **chronic disease** associated with autoimmunity that results from the destruction of pancreas' insulin-producing beta cells.
- Represents 5-10% of total diabetes cases (est. >4-6 million worldwide)
- Prevalence of T1D is approximately 1 in 300 in the US by 18 years of age.
- 85% of all T1D diabetes cases have an onset in people under 20 years-old
- Treatments focused on managing glycaemia by insulin injections
- $6.6bn worldwide sales in 2013; Market growth driven by approval of T2D drugs for T1D (GLP-1s RAs and SGLT-2 inhibitors)

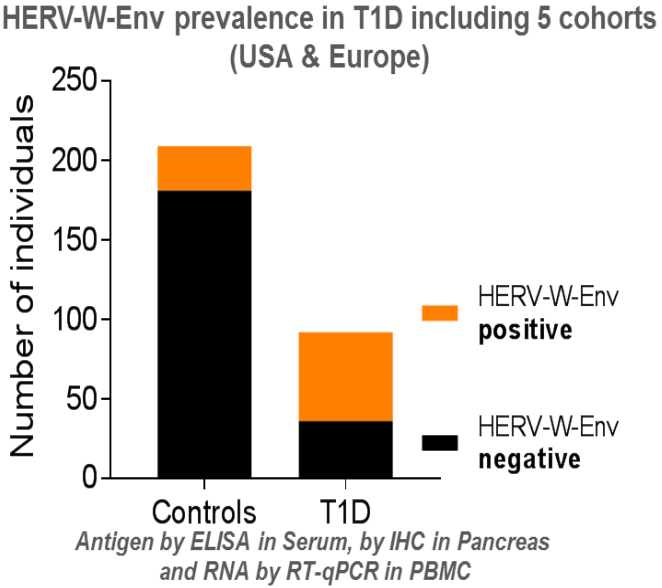
- **No disease modifying therapies** available today
- Several debilitating complications associated with insulin replacement, a life-long treatment
  - >50% of adults with T1D have an A1C >8%
  - Severe consequences of poor glucose level control include renal, ophthalmic, cardiac, vascular and nervous system dysfunctions and deficiencies
  - Significant risk of coma and death by hyperglycemia or hypoglycemia
- Preservation of remaining insulin production :
  - Residual β-cell function may prevent ketoacidosis for many years
  - Preservation of endogenous insulin production is the best prognosis against T1D co-morbidities

Sources: NIH - Genetics Home reference; JDRF.org; WHO; Endocrinol Metab Clin North Am. D. Maahs et al., 2010

June 2019

Data support the hypothesis of a causal role of pHERV-W Env in T1D

- Found in the pancreas of over 70% of T1D patients post-mortem. About 60% in blood.
- Dose dependent disruption of insulin production in vitro by pHERV-W Env
- Induction of hyperglycemia and hypoinsulinemia by pHERV-W Env protein in young HERV-W env transgenic mice
- Preliminary results show that Coxsackie virus type B 4E2 strain upregulates pHERV-W Env expression

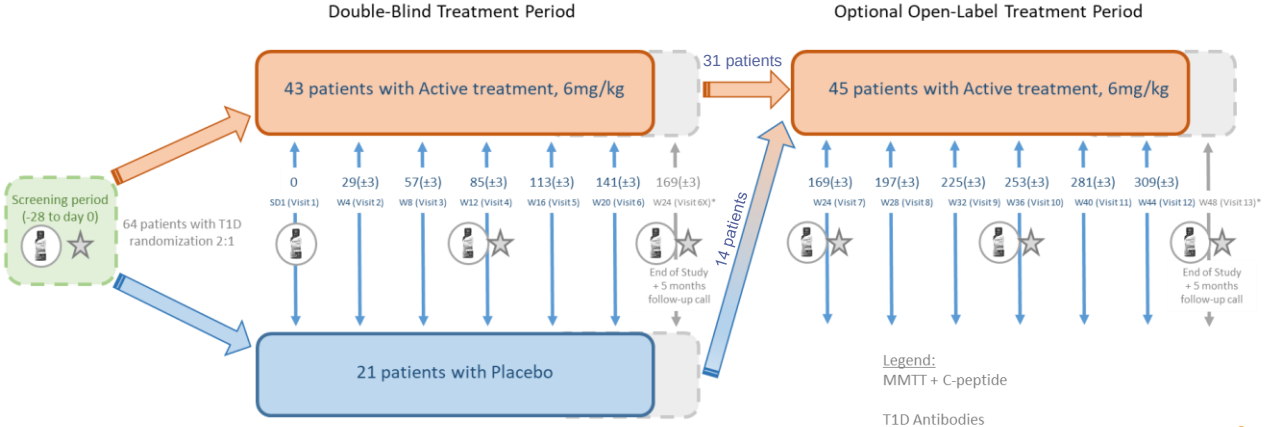


Sources: An ancestral retroviral protein identified as a therapeutic target in type-1 diabetes, S. Levet et al., JCI Insights, September 2017; JDRF/nPOD 2017 Meeting, Fort Lauderdale, USA. ADA 2017 meeting, San Diego, USA.

June 2019

RAINBOW-T1D: Phase IIa to assess safety and pharmacodynamics in an adult T1D population

- A 6-month double-blind placebo-controlled study to assess safety and pharmacodynamics in an adult T1D population ;
  - Double Blind Period Weeks 1-24: 1 active (temelimab 6mg/kg) group vs. placebo
  - Open Label Period Weeks 25-48: 1 active dose group (placebo patients switched to temelimab)
- 64 male and female patients, 18–55 years, with T1D diagnosed in the 4 years prior to signed ICF
- Peak stimulated C-peptide of ≥ 0.2nmol/L; HbA1c ≤ 9%; >1 diabetes-associated auto-antibody



Week 48 Safety Outcomes in adult T1D population

Temelimab remains is very well tolerated over 48 weeks

	Temelimab/- (N=12)	Temelimab/ temelimab (N=31)	Placebo/- (N=7)	Placebo/ temelimab (N=14)	Overall (N=64)
Serious adverse events (SAEs)	0	3	1	3	7
Serious related AEs	0	0	0	1*	1
Number of patient with at least one AE (%)	10 (83.3%)	28 (90.3%)	6 (85.7%)	13 (92.9%)	57 (89.1%)
AEs leading to early termination	0	2	0	0	2
AEs leading to death	0	0	0	0	0

*headache occuring during the placebo period

Week 48 PD Outcomes - Hypoglycemia

Confirmed decrease of hypoglycemic episodes

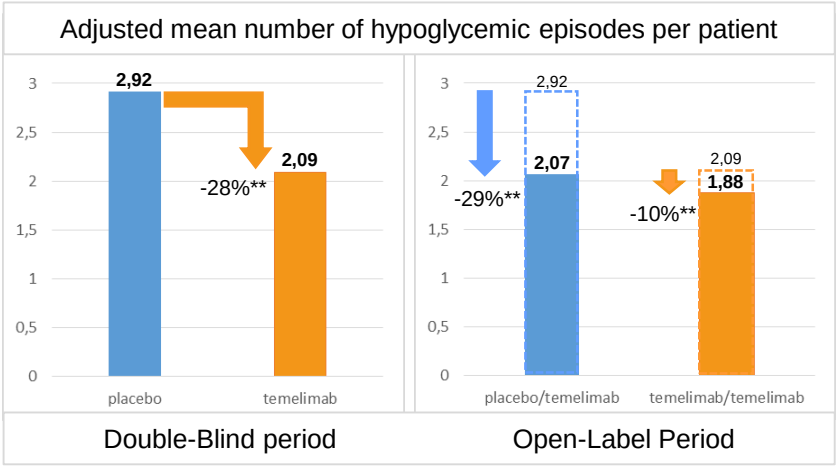
Adjusted mean number of hypoglycemic episodes per patient	Temelimab/temelimab (N=31 out of 43**)	Placebo/temelimab (N=14 out of 21**)	Rate ratio	P-value*
Double-blind Period	2.09	2.92	0.75	0.0001
Extension Period	1.88	2.07	0.91	0.82

Group treated by temelimab 12 months:

- Reduction of frequencies of hypoglycemia under temelimab in first 6-month (-28%, p<0.0001 vs placebo),
- Further reduction of 10% in the second 6 month period

Group switching to temelimab from placebo:

- Reduction of hypoglycemia frequency in this group vs the previous placebo period (-29%), reaching the level of reduction observed with temelimab in the first 6 months of treatment



* Poisson regression analysis

** Patients who continued in the Open-Label period

RAINBOW-T1D Summary

Successful study, opening way to early-onset T1D trials

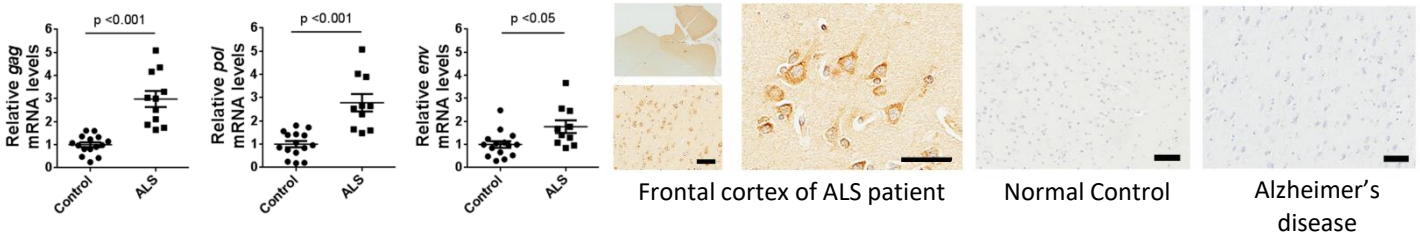
- 12 month study with a 6-month double blind period and a 6-month extension with all patients on temelimab, including patients previously on placebo
- Excellent safety / tolerability of temelimab observed over one year
- Positive temelimab pharmacodynamic observations at 6 months are confirmed in the second period
- No conclusions possible on C-peptide, insulin consumption and HbA1C: small cohort size from a late onset adult population, well treated with low insulin needs, stable during trial
- Study completes its objective of demonstrating safety and pharmacodynamic response in adult T1D patients, opening door to further development in larger early-onset pediatric population

Part 3

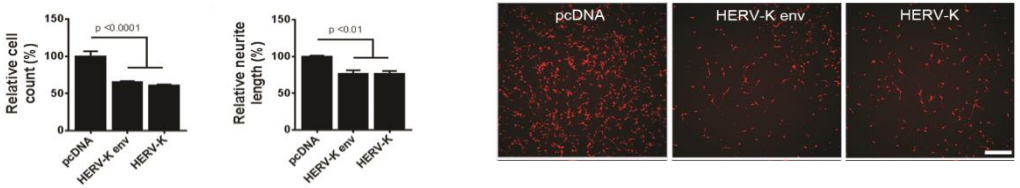
GeNeuro development in ALS

HERV-K Env is upregulated in ALS, and toxic to neurons

- HERV-K (HML-2) is expressed significantly higher in brain tissue of ALS patients than in healthy controls or other neurological disorders



- Expression of HERV-K in neurons is toxic



HERV-K env decreases number of neurons
and reduces relative neurite length

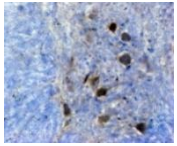
- Genetic investigations reveal that there is dysregulation of HERV-K in a subset of patients with sporadic ALS

Source: Li, Lee, et al., Science Translational Medicine 2015

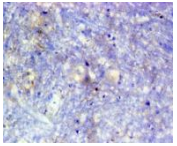
In vivo validation of the HERV-K concept in ALS through transgenic mice

- NINDS developed a transgenic mouse that expresses HERV-K Env in the brain and spinal cord (neurons)

HERV-K

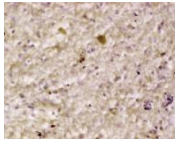


transgenic

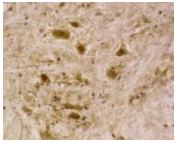


Wild type

chAT + motor neurons

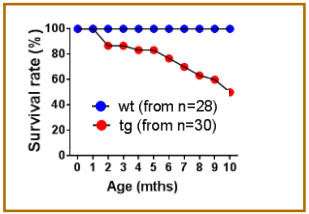


transgenic

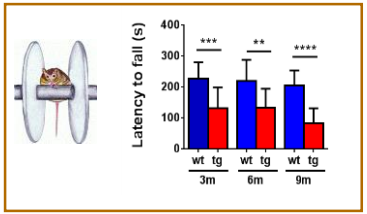


Wild type

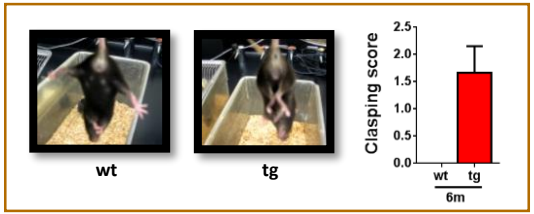
- The phenotype of the transgenic mouse mimics signs and symptoms of clinical ALS



Reduced life span



Motor neuron functionality



Clasping behavior

Source: Li, Lee, et al., Science Translational Medicine 2015

Status of the ALS project

- Research partnership in 2017 with the National Institute of Neurological Disorders and Stroke (NINDS), part of the U.S. National Institutes of Health (NIH)
  - GeNeuro provides antibodies designed to block the activity of HERV-K envelope protein
  - NINDS tests antibodies in cellular and animal models of HERV-K associated ALS
  - Results validate the potential of GeNeuro's anti pHERV-K antibodies as a new therapeutic approach against ALS

- Following successful results of the research partnership with NIH in ALS models, GeNeuro has signed in October 2018 an exclusive worldwide license with the NIH covering the development rights of an antibody program to block the activity of pHERV-K Env, a potential key factor in the development of ALS

- **GeNeuro has launched the preclinical development of the lead antibody, aiming at IND by mid-2020**

Part 4

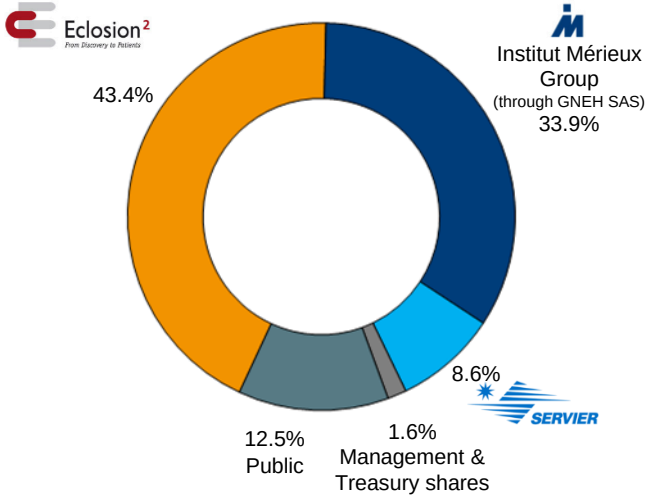
Good basis for growth

The GeNeuro team

	**Jesús Martin-Garcia** | MBA Chief Executive Officer – Co-founder	**Strong track-record in creating value in high technology start-ups**	More than 20 years of experience as founder and investor in successful startups	MBA from Harvard Business School
	**Dr. François Curtin** | MD, MPhil, MBA Chief Operating Officer	**15 years experience in MS, in charge of R&D and clinical development**	Clinical expertise at Merck Serono, previously at Swissmedic (“Swiss FDA”)	MD from Geneva Medical School & MBA from Warwick Business School
	**Dr. Hervé Perron** | PhD, HDR Chief Scientific Officer – Co-founder	**Made the initial key discoveries in the field of human endogenous retroviruses while at INSERM and bioMérieux**	Has published over 120 peer-reviewed papers and patents, mostly on HERVs	PhD in virology and a professorial thesis in neuroimmunology
	**Dr. Robert Glanzman** | MD Chief Medical Officer	**Over 20 years of clinical, medical affairs and clinical development experience in MS**	13 years as Medical Affairs/Clinical Development Leader at Pfizer, Novartis and Roche. Global Development Lead for Ocrelizumab Phase III	MD with Residency in Neurology from the University of Michigan
	**Dr. Thomas Rückle** | PhD. PMP SVP, Head of Preclinical Development	**Over 20 years experience in translational science**	Preclinical and early clinical expertise at Merck Serono & MMV. As project director, led several projects from lead to Phase II clinical proof of concept	PhD in Organic Chemistry
	**Miguel Payró** Chief Financial Officer	**Experience in international groups & expertise as CFO of a Swiss listed company in the medical sector**	Previously CFO of Groupe Franck Muller & Unilabs, among others	Degree in business administration from the University of Geneva

Financial Summary

Share capital as of May 2019



Note: excludes stock options and performance-based option units, representing a maximum 6.9% dilution, with an average exercise price of €10.38 per share

P&L and cash balance (in € '000)

	1Q 2019	FY 2018	FY 2017	FY 2016
Income	n.a.	7,463	14,949	5,918
R&D Expenses	n.d.	(10,930)	(16,161)	(14,419)
G&A	n.d.	(4,686)	(4,597)	(5,535)*
Operating loss	n.d.	(8,089)	(5,740)	(14,037)
Cash & Equivalents	13,300**	16,461**	26,602	34,489

Notes: * 2016: includes €1,801k of IPO-related fees
** : pro forma, including €7.5 mln line of credit facility with GNEH SAS established Dec. 2018 – of which €2,5 mln was drawn at end of 1Q

Value enhancing milestones in early 2019

- ✓ Phase Ic testing higher doses of temelimab for further development 1Q2019
- ✓ ANGEL-MS (2 year results) 1Q2019
- ✓ T1D Phase IIa full 12-month results 2Q2019
- Partnership discussions on temelimab in MS

Capturing the full value of the HERV platform

- Cash to deliver on ongoing programs – funded mid-2020
  - MS: ANGEL-MS results – Phase Ic testing safety of higher doses of temelimab
  - T1D: 12-month results of RAINBOW trial with temelimab
  - ALS: preclinical development of new monoclonal antibody against pHERV-K
- Open options for development going forward in MS
  - Partnering discussions ongoing
  - Confirmatory trial to find optimal dose in target non-active progressive population, potentially supporting registration
- Open options for development in other indications, alone or with partners
  - Phase IIb in T1D in a juvenile population
  - IND for anti pHERV-W new monoclonal antibody planned for mid-2020

Targeting the cause of neurodegenerative and autoimmune diseases

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