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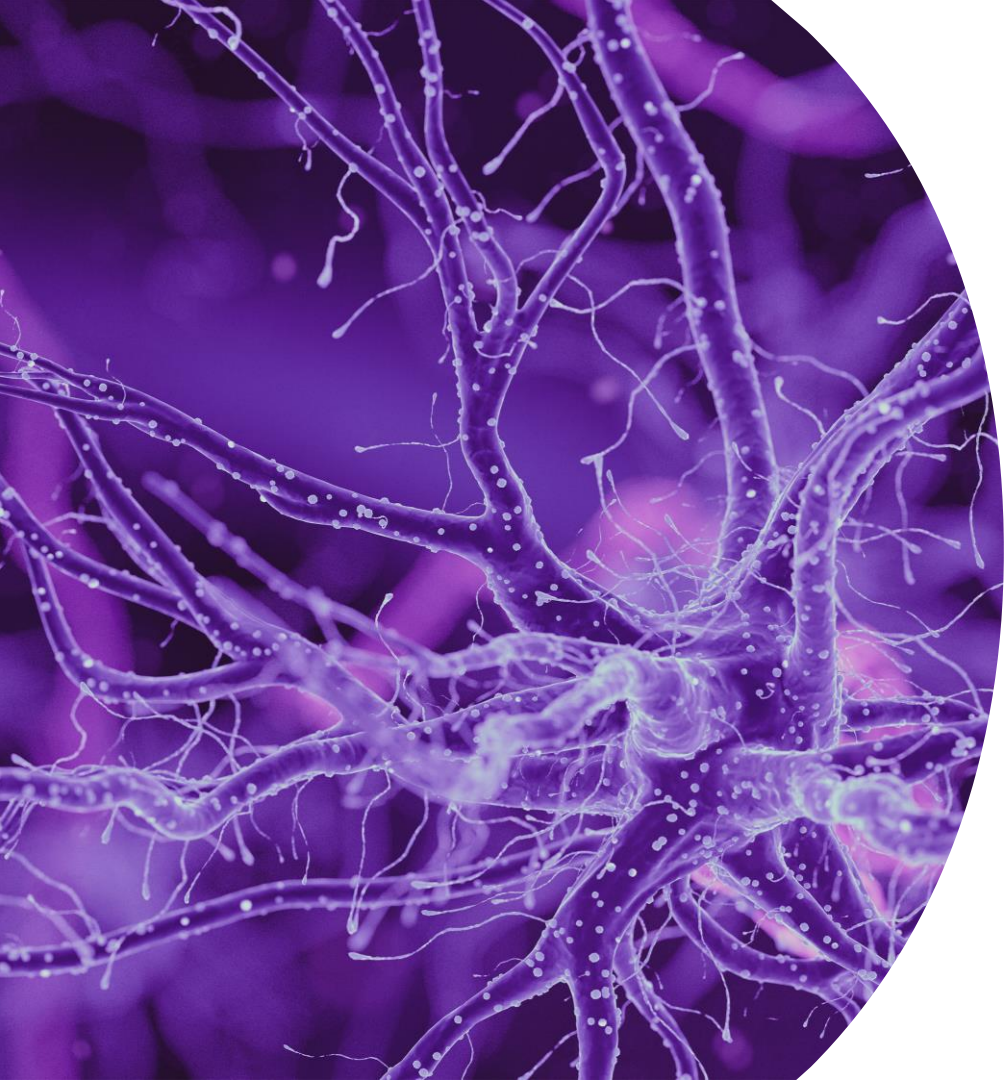

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Tolebrutinib Investor Call

ACTRIMS Forum 2022

February 24-26 | West Palm Beach, Florida

February 25, 2022

Forward-looking statements

This document contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts. These statements include projections and estimates and their underlying assumptions, statements regarding plans, objectives, intentions and expectations with respect to future financial results, events, operations, services, product development and potential, and statements regarding future performance. Forward-looking statements are generally identified by the words "expects", "anticipates", "believes", "intends", "estimates", "plans" and similar expressions. Although Sanofi's management believes that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Sanofi, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including post marketing, decisions by regulatory authorities, such as the FDA or the EMA, regarding whether and when to approve any drug, device or biological application that may be filed for any such product candidates as well as their decisions regarding labelling and other matters that could affect the availability or commercial potential of such product candidates, the fact that product candidates if approved may not be commercially successful, the future approval and commercial success of therapeutic alternatives, Sanofi's ability to benefit from external growth opportunities, to complete related transactions and/or obtain regulatory clearances, risks associated with intellectual property and any related pending or future litigation and the ultimate outcome of such litigation, trends in exchange rates and prevailing interest rates, volatile economic and market conditions, cost containment initiatives and subsequent changes thereto, and the impact that COVID-19 will have on us, our customers, suppliers, vendors, and other business partners, and the financial condition of any one of them, as well as on our employees and on the global economy as a whole. Any material effect of COVID-19 on any of the foregoing could also adversely impact us. This situation is changing rapidly, and additional impacts may arise of which we are not currently aware and may exacerbate other previously identified risks. The risks and uncertainties also include the uncertainties discussed or identified in the public filings with the SEC and the AMF made by Sanofi, including those listed under "Risk Factors" and "Cautionary Statement Regarding Forward-Looking Statements" in Sanofi's annual report on Form 20-F for the year ended December 31, 2021. Other than as required by applicable law, Sanofi does not undertake any obligation to update or revise any forward-looking information or statements.

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Introduction

Dietmar Berger, MD PhD

Global Head of Development, CMO

Agenda

ACTRIMS Investor Call

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Dietmar Berger, MD PhD
Global Head of Development, CMO

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Tom Snow,
Global Franchise Head, Neurology

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Therapeutic Area Head, Multiple Sclerosis

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Professor and Research Chair of the MS Society of Canada at the University of British Columbia, Vancouver

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Tim Turner, PhD
Global Project Head, Tolebrutinib

06 **Q&A**

Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

Significant progress made in *neurology* since 2020

Key achievements

Initiated four Phase 3 trials of **tolebrutinib** across the full spectrum of **MS**

Initiated Phase 3 study of **tolebrutinib** in **Myasthenia Gravis**

Initiated Phase 2 study of **SAR441344**[1] (anti-CD40L mAb) in relapsing **MS**

Initiated Phase 2 study of **SAR445088**[2] (anti-serine C1s mAb) in **CIDP**

- FDA Orphan Drug Designation granted

Completed Phase 1 study of **SAR443820**[3] (RIPK1i) in **ALS**

- FDA Fast Track Designation granted

Acquisitions / Collaborations

PRINCIPIA BIOPHARMA

DENALI THERAPEUTICS

ablbio medicine for a better life

INTERNATIONAL PROGRESSIVE MS ALLIANCE
More than hope. Progress.

Parkinson's Foundation

(1) Developed in collaboration with Immunext. (2) Formerly known as BIVV020. (3) Also known as DNL788, developed in collaboration with Denali.
These products are currently under clinical investigation and their safety and efficacy have not been evaluated by any regulatory authority.

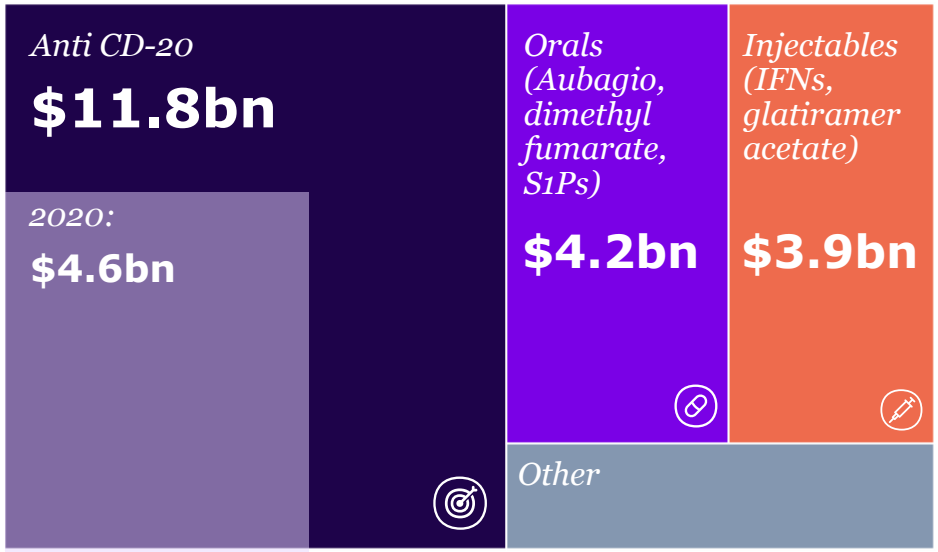
Sanofi in Neurology

Tom Snow

Global Franchise Head, Neurology

Building on a *strong foundation* in MS

Multiple Sclerosis (MS) *market* in 2026e[3]



Sanofi MS *portfolio*

Tolebrutinib target profile

- Investigational brain-penetrant BTKi, designed to treat the entire disease spectrum
- First- and best-in-class potential

Once-daily AUBAGIO® (teriflunomide) 14 mg tablets

- Reliable combination of efficacy, safety, and once-daily oral dosing
- #1 selling oral DMT in the US[1]

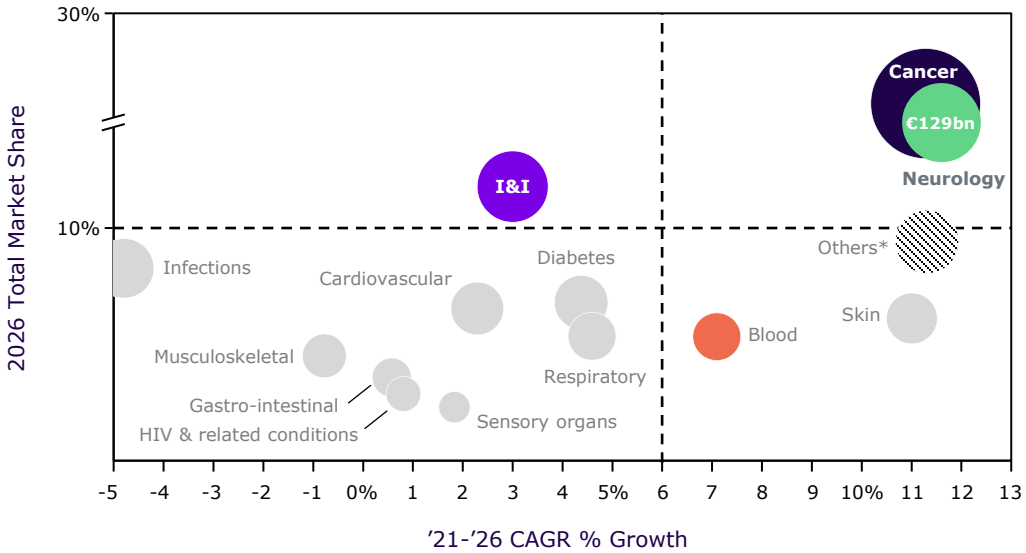
LEMTRADA® alemtuzumab 12mg IV

- Long-term disease control in the absence of continuous dosing
- >24,000 patients currently controlled[2]

(1) IQVIA, Dec 2021. (2) Patients previously dosed with Lemtrada and did not require additional Lemtrada doses in 2021 - potential discontinuations not included – Source: Sanofi analysis. (3) Evaluate Pharma (as of February 11, 2022).
Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

With *high unmet need* and *rapidly advancing science*, Neurology represents a highly attractive opportunity

Projected to be a key driver of industry growth[1]



High burden of disease

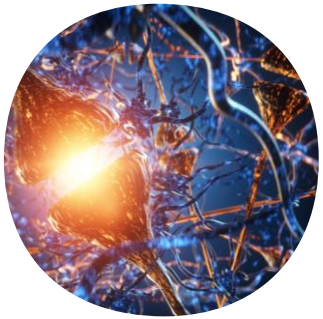
Rapidly advancing science

New enabling technologies

Engaged stakeholders

(1) Evaluate Pharma, January 2022.

Targeted strategic approach



Neuroinflammation

Multiple sclerosis

Myasthenia gravis

CIDP

Neurodegeneration

ALS

Synucleinopathies: Parkinson's Disease, Multiple System Atrophy

Tauopathies: Alzheimer's Disease, Progressive Supranuclear Palsy

Genetic Disorders

Monogenic Neurological Disorders

Neuromuscular Disorders

Complex Neurological Disorders

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Neurology Pipeline Overview

Erik Wallstroem, MD PhD

Therapeutic Area Head, Multiple Sclerosis

Clinical pipeline

Neuroinflammation

Compound	Description	Target indication	Phase	Planned submission
Tolebrutinib	BTK inhibitor	Relapsing Multiple Sclerosis	3	2024
Tolebrutinib	BTK inhibitor	Primary Progressive Multiple Sclerosis	3	2025
Tolebrutinib	BTK inhibitor	Secondary Progressive Multiple Sclerosis	3	2025
Tolebrutinib	BTK inhibitor	Myasthenia Gravis	3	2025
SAR445088[1]	Complement C1s inhibitor	Chronic Inflammatory Demyelinating Polyneuropathy	2	
SAR441344[2]	Anti-CD40L mAb	Multiple Sclerosis	2	
SAR443820/DNL788[3]	RIPK1 inhibitor	Multiple Sclerosis	1	

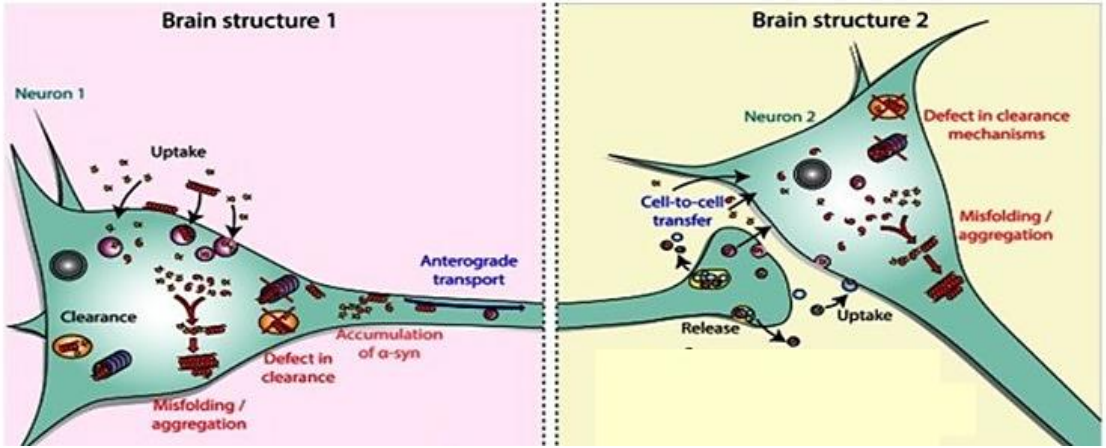
Neurodegeneration

Compound	Description	Target indication	Phase
SAR443820/DNL788[3]	RIPK1 inhibitor	Amyotrophic Lateral Sclerosis	1
SAR443820/DNL788[3]	RIPK1 inhibitor	Alzheimer's Disease	1 (opt-in)
ABL301[4]	Anti-alpha-synuclein and IGF1R bispecific Ab	Parkinson's Disease	preclinical

(1) Formerly known as BIVV020. (2) Developed in collaboration with Immunext. (3) Developed in collaboration with Denali. (4) Developed in collaboration with ABL Bio.
These products are currently under clinical investigation and their safety and efficacy have not been evaluated by any regulatory authority.

Potential first in class *bi-specific alpha-synuclein antibody* for Parkinson's Disease

Donor neuron *Acceptor neuron*



Goedert et al. 2017 Brain 140:266; George et al Brain Pathology 23(3):350-7

Sanofi's global collaboration and license agreement with ABL Bio, **announced January 2022**, includes development of ABL301 for treatment of Parkinson's disease (PD) and Multiple System Atrophy (MSA)

ABL301 is a potential first-in-class bispecific antibody that targets alpha-synuclein, with a *brain penetrant shuttle*

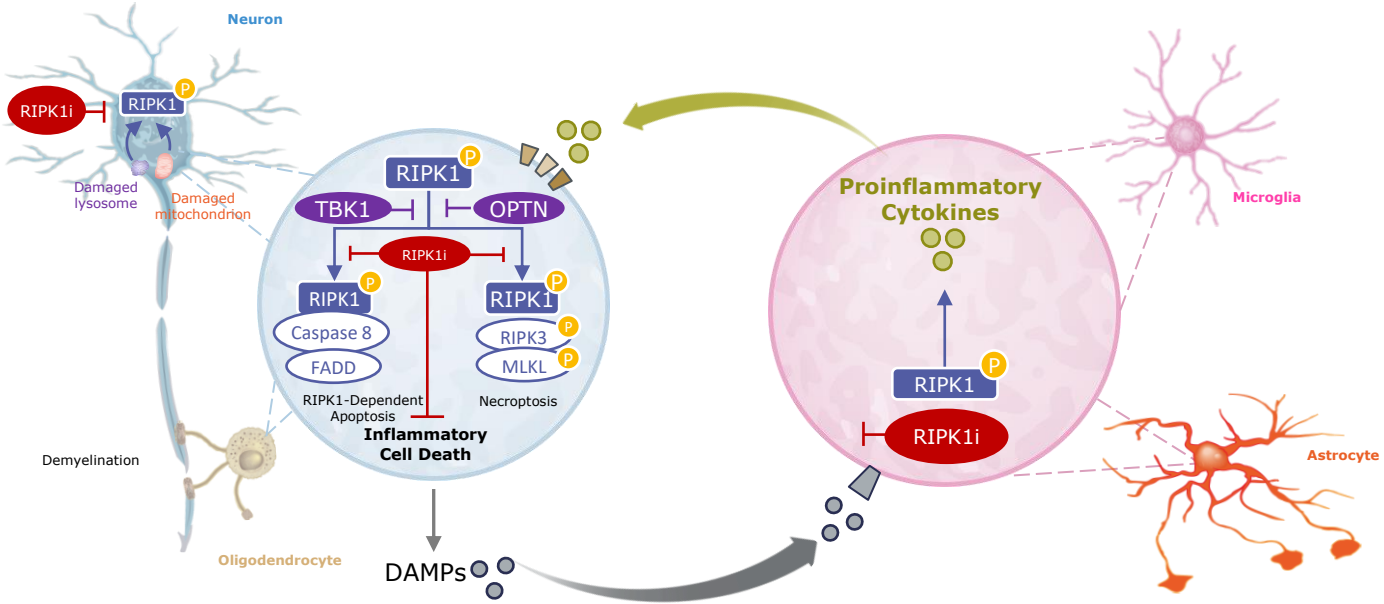
Brain shuttle targeting insulin-like growth factor 1 receptor

Anti-alpha-synuclein domain with robust recognition of *pathological aggregates* (pre-formed fibrils)

By blocking the transcellular spread of alpha-synuclein, ABL301 may *block progression* of pathology

In addition, ABL301 antibody may target *intraneuronal alpha-synuclein aggregates*

RIPK1-inhibitor *SAR443820*



Proposed impact on inflammation and degeneration

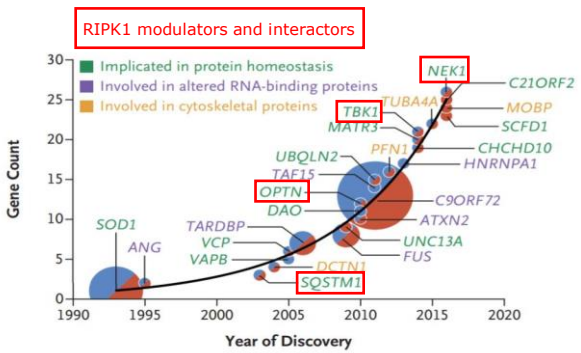
Left: RIPK1 inhibition abrogates inflammatory cell death and promotes survival of *neurons* and *oligodendrocytes*[1]

Right: RIPK1 inhibition reduces *microglial activation* and *proinflammatory cytokine* production by glial cells[2,3,4].

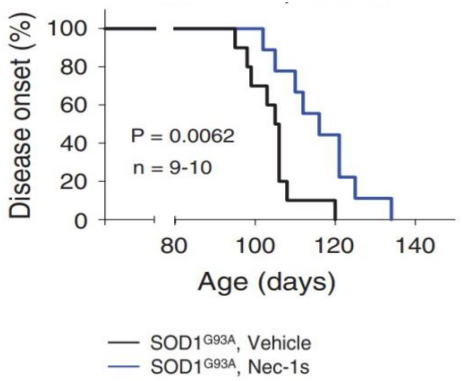
(1) Yuan et al, Nat Rev Neurosci. 2019;20:19–33; (2) Zelic et al., Cell Reports. 2021;35:109-12; (3) Mifflin et al., Nat Rev Drug Discov.2020;19:553-71. (4) Ito et al., Science. 2016;353:603-8.
DAMPs: Damage-Associated Molecular Patterns; FADD: Fas-Associated protein with Death Domain; MLKL: Mixed Lineage Kinase domain-Like protein; OPTN: Optineurin; P: Phosphorylation; RIPK1: Receptor-Interacting serine/threonine-Protein Kinase 1; RIPK1i: Receptor-Interacting serine/threonine-Protein Kinase 1 inhibitor; RIPK3: Receptor-Interacting serine/threonine-Protein Kinase 3; TBK1: Tank-binding Kinase 1.

Genetic, model and human tissue rationale for *RIPK1 inhibition* in ALS

Genetics of ALS are enriched in RIPK1 interactors[1]

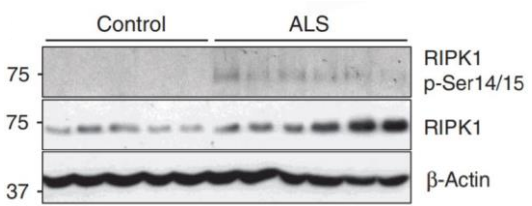


RIPK1 inhibition in a mouse model of ALS (SOD1G93A model)[2]



RIPK1 activation is prominent in ALS patient derived tissue[2]

Western blot analysis of human post-mortem spinal cord samples



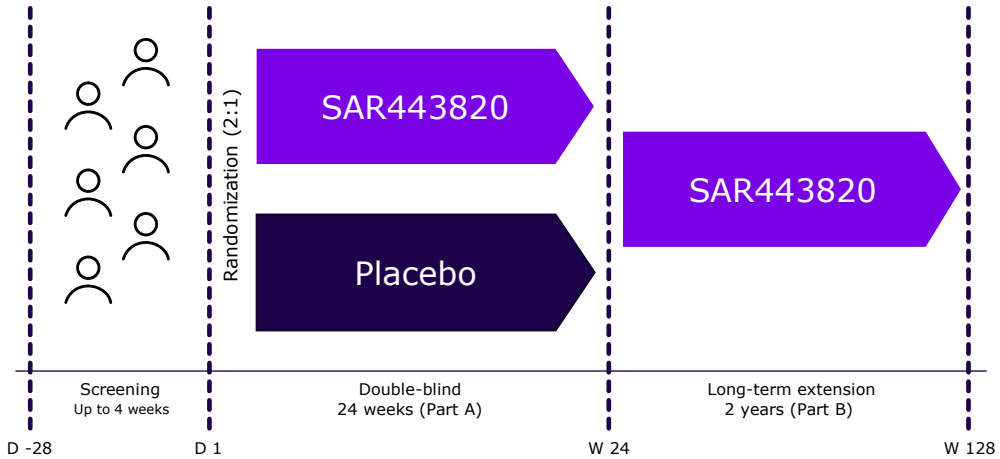
Increased RIPK1 activation (pS166 RIPK1) and expression was also detected by MSD assay in post-mortem spinal cord samples[2]

(1) Brown and Al-Chalabi, N Engl J Med. 2017;377:162-72; 2. Ito et al., Science. 2016;353:603-8. (2) Sanofi Genzyme, data on file.

ALS: Amyotrophic Lateral Sclerosis; MSD: Meso Scale Discovery; Nec-1s: Necrostatin-1s; NEK1: Never-in-mitosis A related protein Kinase 1; OPTN: Optineurin; RIPK1: Receptor-Interacting serine/threonine-Protein Kinase 1; SOD1: Superoxide Dismutase; SQSTM1: Sequestosome-1; TBK1: Tank-Binding Kinase 1.

Phase 2 Trial of *SAR443820* in ALS (n=261)

Study design:



Study type:

Phase 2, multi-center, randomized, double-blind, placebo-controlled study followed by an open-label long-term extension period

Primary endpoint:

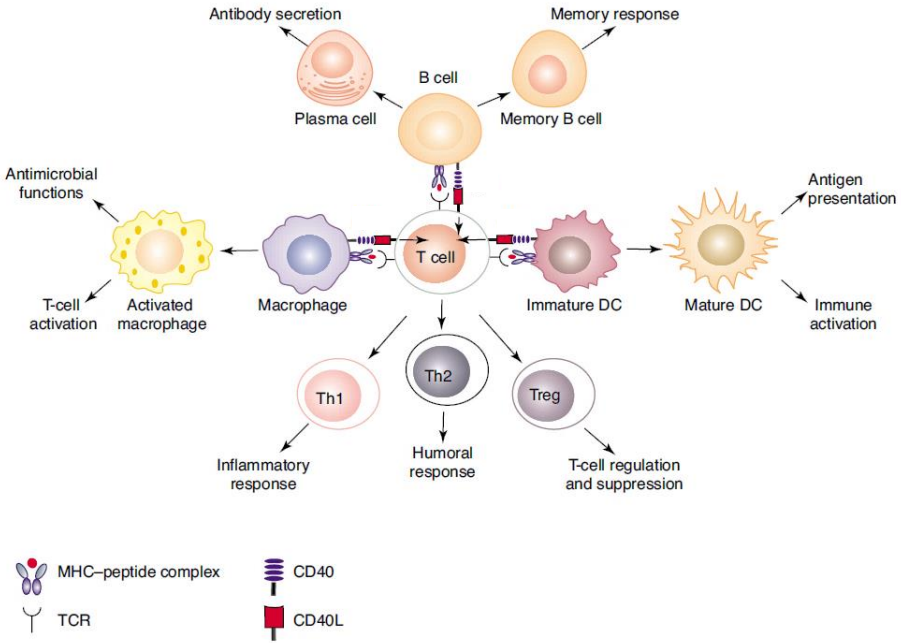
Change in ALS progression (ALSFRS-R score)

Secondary endpoints:

- Combined Assessment of Function and Survival (CAFS score)
- Respiratory function (SVC)
- Muscle strength (HHD)
- Quality of Life (ALSAQ-5)
- Plasma Neurofilament Light chain (NfL)
- Safety and tolerability
- Pharmacokinetics

ALS: Amyotrophic Lateral Sclerosis; ALSAQ-5: ALS Assessment Questionnaire; ALSFRS-R: ALS Functional Rating Scale-Revised; D: Day; HHD: Handheld Dynamometry; SVC: Slow Vital Capacity; W: Week.

Anti-CD40L *SAR441344*



(1) Mathur RK et al. *Trends Parasitol*. 2006;22(3):117-122.
APC: Antigen-Presenting Cell; DC: Dendritic Cell; MHC: Major Histocompatibility Complex; MS: Multiple Sclerosis; NO: Nitric Oxide; TCR: T-cell Receptor; TNF: Tumor Necrosis Factor.

A pleiotropic approach to MS therapy

CD40L, a member of the TNF family is the classical ligand for CD40; targeting the CD40-CD40L co-stimulatory pathway could affect inflammation in MS via blockade of several interrelated mechanisms[1].

- Suppression of *T-cell co-stimulation* and *differentiation* of effector cells
- Suppression of the *antigen presentation function*, germinal center formation, class switching, affinity maturation, antibody production, and generation of long-lived plasma cells/memory cells in B cells
- Suppression of *pro-inflammatory cytokine secretion* (TNF-α, IL-12), NO, and reduction of antigen presentation capacity (reactivating T cells) in macrophages
- Suppression of *maturation*, thereby regulating APC function and induction of immune activation in dendritic cells

Potential for a *personalized* treatment approach

Literature

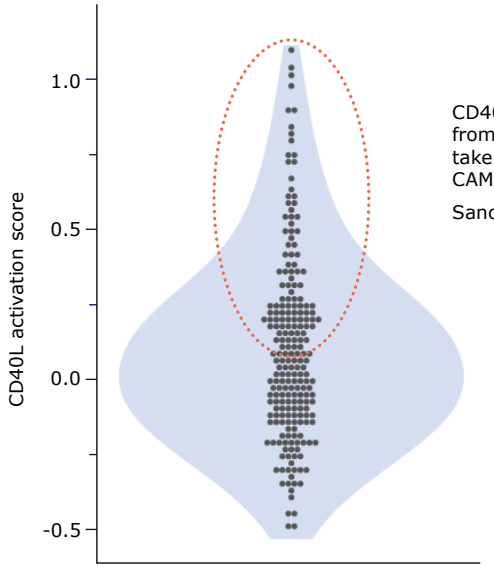
- Indication of the possibility of a *biomarker approach* to segment the population
- Highest needs are in the progressive forms of MS

Druggable genetic targets associated with multiple sclerosis prioritized by multi-omic SMR

Chromosome	Methylation probe	Ensembl gene ID	Gene	Druggability tier	Replicated in CAGE
20	cg01943874	ENSG00000101017	CD40	Tier 1	Yes
20	cg17929951	ENSG00000101017	CD40	Tier 1	Yes
20	cg19785066	ENSG00000101017	CD40	Tier 1	Yes
20	cg21601405	ENSG00000101017	CD40	Tier 1	Yes
20	cg25239996	ENSG00000101017	CD40	Tier 1	Yes
2	cg04202892	ENSG00000153208	MERTK	Tier 1	Yes
2	cg08443563	ENSG00000153208	MERTK	Tier 1	Yes
2	cg18646521	ENSG00000153208	MERTK	Tier 1	Yes
1	cg23712594	ENSG00000143799	PARP1	Tier 1	Yes

Source: Jacobs at al, Brain Communications 2020

Biomarker data



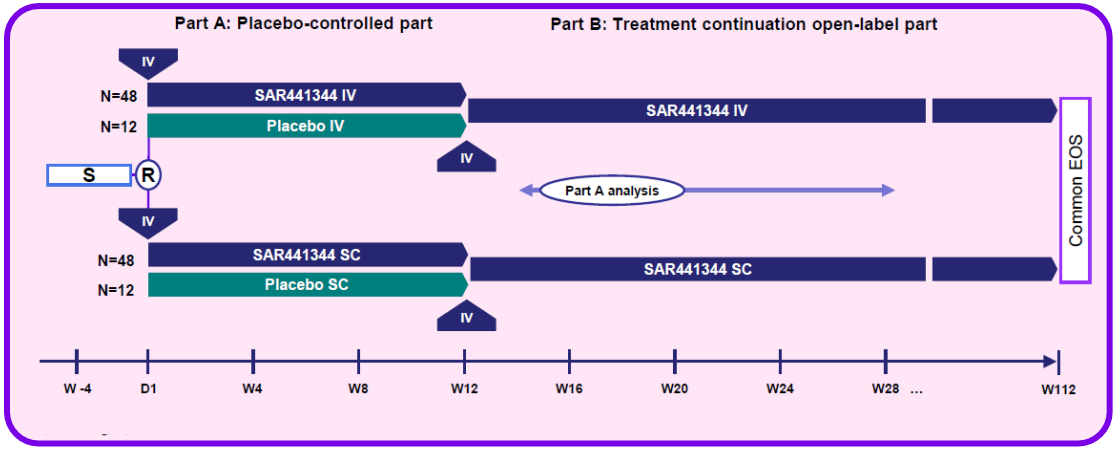
CD40L activation data is from 216 RRMS patients taken at baseline in the CAMMS study.

Sanofi data on file.

MS: Multiple Sclerosis; RRMS: Relapsing-Remitting Multiple Sclerosis; SMR: Summary based Mendelian Randomization.

Phase 2 trial of *SAR441344* in MS (n=120)

ACT16877 study design



Last updated on clinicaltrials.gov September 16, 2021
ClinicalTrials.gov identifier: NCT04879628. https://clinicaltrials.gov/ct2/show/NCT04879628

Primary endpoint:

- Number of new Gd-enhancing T1-hyperintense lesions at the Week 12 as measured by brain MRI

Secondary endpoint:

- Number of new or enlarging T2 lesions at Week 12
- Total number of Gd-enhancing T1 hyperintense lesions at Week 12
- Adverse events, serious adverse events, potentially clinically significant abnormalities in laboratory tests, electrocardiogram, or vital signs during the study period
- PK parameters (maximum concentration [C_{max}], time to C_{max} [t_{max}], area under the curve over the dosing interval ($AUC_{0\text{-}tau}$), and elimination half-life [$t_{1/2z}$]).

N=120 (for at least 100 evaluable, randomization 4:1:4:1). Blinding: double-blind for treatment group, open for dose and route of administration; participants receive either IV or SC.
Participant may switch to the other arm after evaluation of results of Part A, if decided to close 1 arm (this may occur at different time in Part B for individual participant, depending on the time of recruitment to the study).
AUC: Area Under the Curve; EOS: End Of Study; IV: Intravenous; MRI: Magnetic Resonance Imaging; MS: Multiple Sclerosis; R: Randomization; S: Screening; SC: Subcutaneous.

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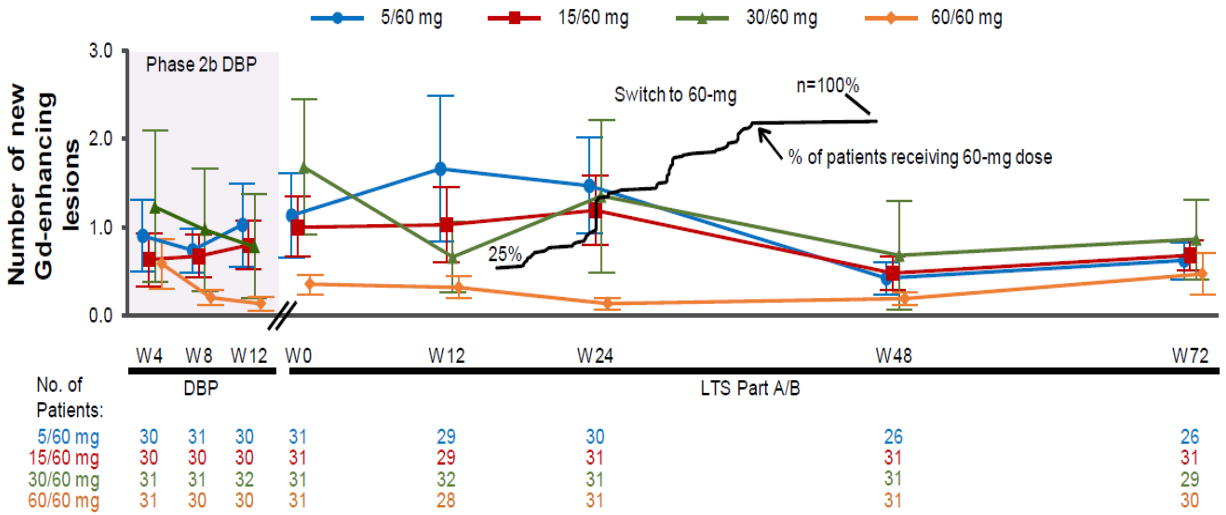
Tolebrutinib 18-month data

Anthony Traboulsee, MD

Professor and Research Chair of the MS Society of Canada at the University of British Columbia, Vancouver

Strong impact on Gd-enhancing lesions and the only BTKi demonstrating long term data on focal lesions

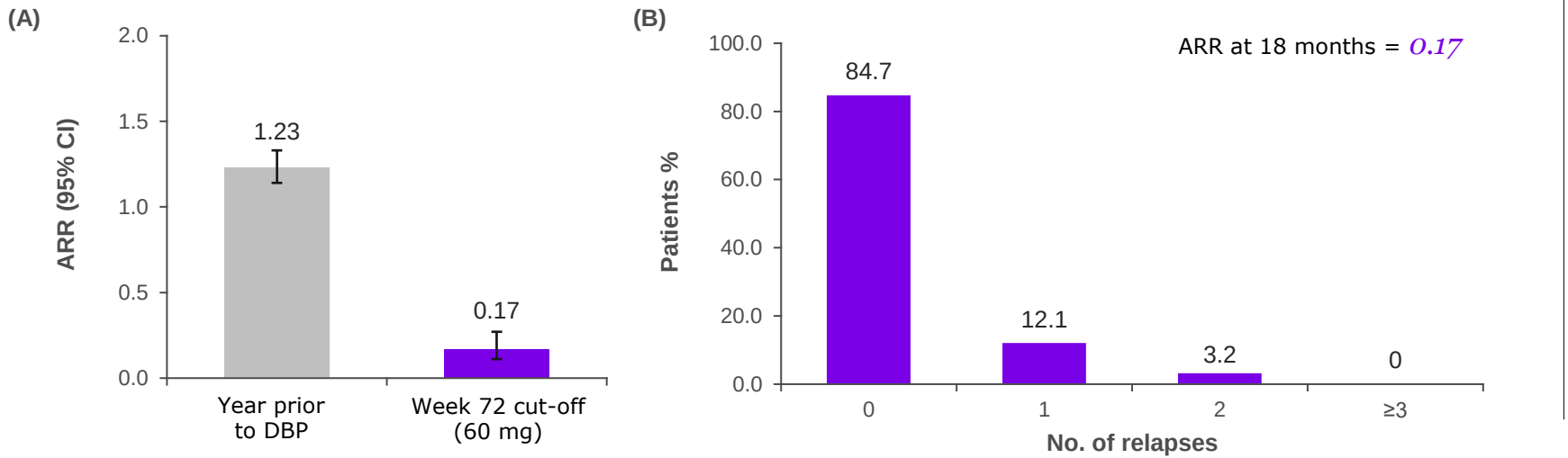


- New Gd-enhancing lesions *remain low* in patients who started on or switched to tolebrutinib 60mg
- T2 lesion volume change *remain low* for the 60/60-mg arm
- Median SEL volume *lowest* (284 [168-504] mm^3) in the 60/60-mg arm

Data are mean (SE). The switches to 60-mg from the lower doses occurred between W15-W47 (the black line shows the percentage of patients receiving the 60-mg dose). DBP: Double-Blind Period; LTS: Long-Term Safety; SEL: Slowly Evolving Lesions. Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

85% of patients remained *relapse-free* at 18 months

ARR (A) and Relapse Frequency (B) up to the LTS Week 72 Cut-off [1]



(1) ARR after ≥8 weeks of tolebrutinib 60 mg treatment in LTS16004 (up to cut-off for analysis).
For patients originally assigned to 5, 15, or 30 mg, only the patient years and relapses starting 8 weeks after the switch to Part B are included. For patients originally assigned to 60 mg, all LTS16004 data are included unless the sum of the DRI15928 placebo run-out period and any gap period to start of LTS16004 Part A was >4 weeks, in which case only the patient years and relapses starting 8 weeks after re-initiation of treatment are included.

Continued *favorable* tolerability and safety profile

Most common TEAEs occurring in ≥5% of patients[1]

TEAE	Patients, n (%)
COVID-19[2]	20 (16)
Headache	16 (13)
Nasopharyngitis	13 (10)
Upper respiratory tract infection	10 (8)
Arthralgia	7 (6)

94%

of patients remained in the study at the 18-month cut-off

(1) All patients (n=125). (2) All cases of COVID-19 were mild (n=11) or moderate (n=9) and resolved, and patients remained in the study. Three of the moderate COVID-19 cases were considered serious, of which 2 were hospitalized. Tolebrutinib treatment was interrupted temporarily in 4 patients. For details, see poster P126.
TEAE: Treatment Emergent Adverse Event.

Conclusion

- Nearly all patients (*94%*) who enrolled in the long-term extension study of tolebrutinib in patients with RMS have *remained* on study as of September 6, 2021 (18-month cut-off).
- New Gd-enhancing lesion counts *remained low* for the tolebrutinib 60-mg arm and were *reduced* in lower dose arms by the LTS study W48/72 when all patients had switched to 60 mg.
- Safety data continue to show favorable *tolerability* without the emergence of any new safety signals.
- ARR in patients on tolebrutinib 60 mg was *low*, and *~85%* of patients were free of relapses. EDSS scores remained *stable*.
- Longer follow-up in the ongoing extension, as well as data from the phase 3 trials, will continue to build on the safety and efficacy profile of tolebrutinib in patients with MS.

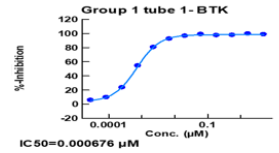
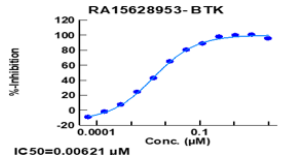
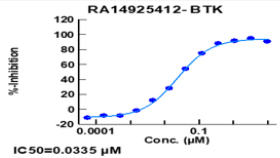
ARR: Annualized Relapse-Rate; EDSS: Expanded Disability Status Scale; MS: Multiple Sclerosis; RMS: Relapsing Multiple Sclerosis.
Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

Tolebrutinib pharmacology

Tim Turner, PhD

Global Project Head, Tolebrutinib

Fast and *potent* BTK inhibition with tolebrutinib

	BTK			
	IC50 (nM)	Conf. Interval 95%	Hill	Curve
tolebrutinib	**0.676**	**0.355**	**1.25**	
fenebrutinib	**6.21**	**9.25**	**0.69**	
evobrutinib	**33.5**	**44.4**	**0.88**	

K_{inact}/K_i = *4.37* $\mu M^{-1} * s^{-1}$

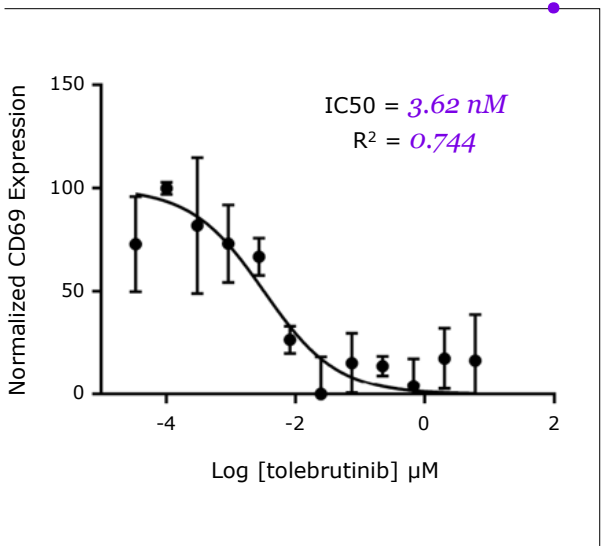
k_1 = *0.00245* $\mu M^{-1} * s^{-1}$

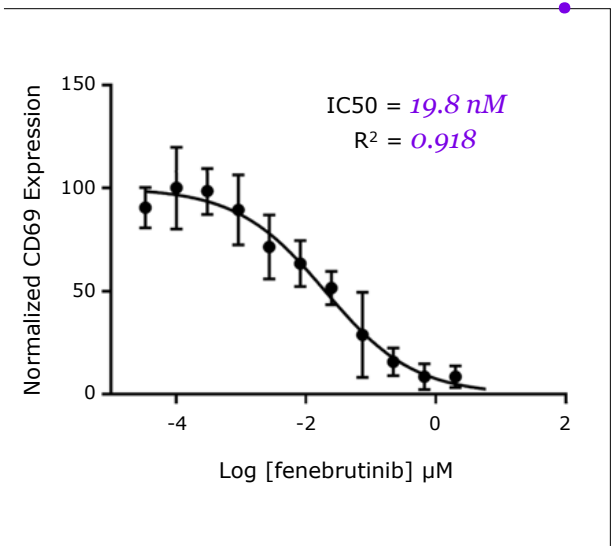
K_{inact}/K_i = *0.068* $\mu M^{-1} * s^{-1}$

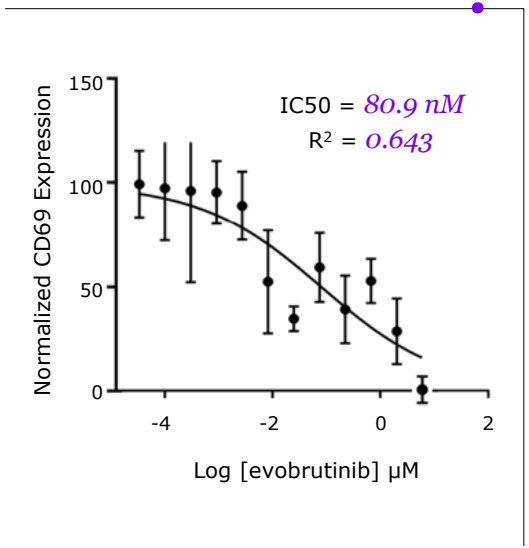
Kinetic experiments revealed that *tolebrutinib* inhibited BTK *64x faster* than evobrutinib, *1,780x faster than fenebrutinib*

Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

B-cell inhibition *consistent* with biochemical results





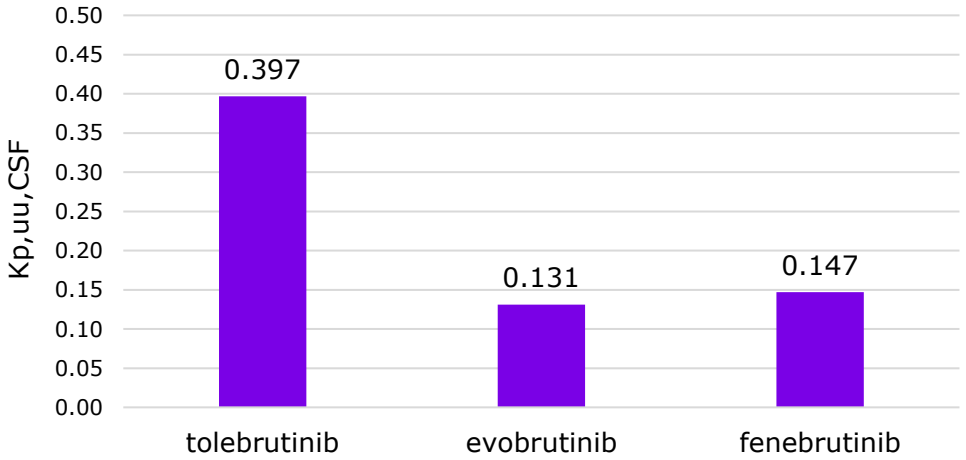


Source: Ramos B Cell data.

Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

Tolebrutinib demonstrated intrinsically *superior* brain penetrance in non-human primates

Comparison of Kp,uu,CSF on Day 4 at 10 mg/kg

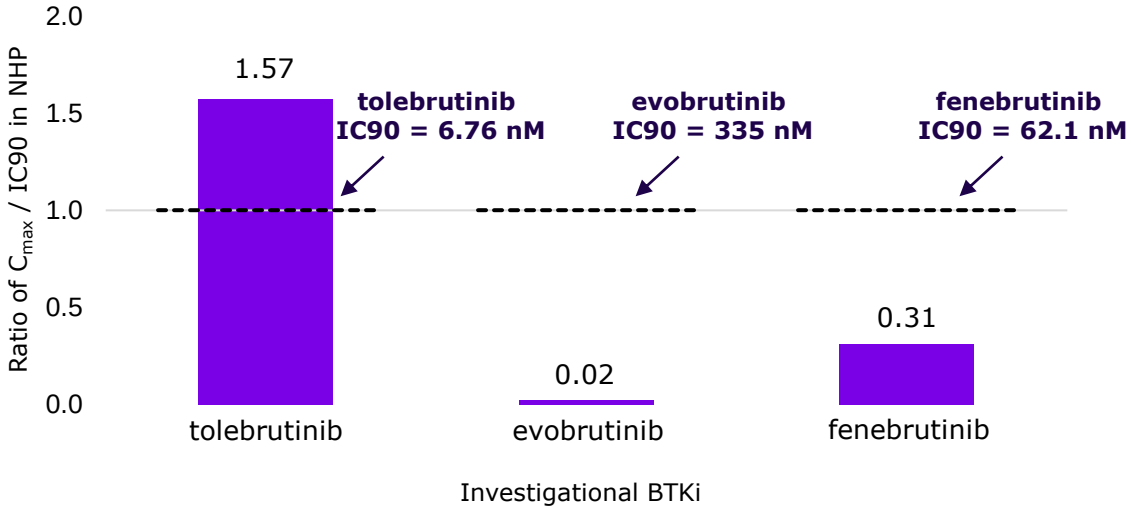


BTK inhibitor	AUC, CSF (h*ng/mL)	Cmax, CSF (ng/mL)
tolebrutinib	19.6	4.84
evobrutinib	10.8	3.20
fenebrutinib	62.3	12.9

AUC: Area Under the Curve; CSF: Cerebrospinal Fluid.
Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

Conclusion

Only tolebrutinib exceeded the IC90 value in CSF



- Tolebrutinib was *more potent* in terms of BTK inhibition than evobrutinib (*50x*) or fenebrutinib (*9.3x*). Relative potency to inhibit B-cell activation was consistent with biochemical results.
- Tolebrutinib demonstrated *intrinsic CNS penetrance* in non-human primates, based on the unbound partition coefficient (*0.397*), approximately *3x* higher than evobrutinib (*0.131*), fenebrutinib (*0.147*).
- The combination of high potency, reaction rates, and CNS exposure suggested that tolebrutinib inhibits BTK signaling in the CNS by *>90%*, consistent with *pharmacological activity in the brain and spinal cord*.

CNS: Central Nervous System.
Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.

Q&A session

Dietmar Berger, MD PhD
Global Head of Development, CMO

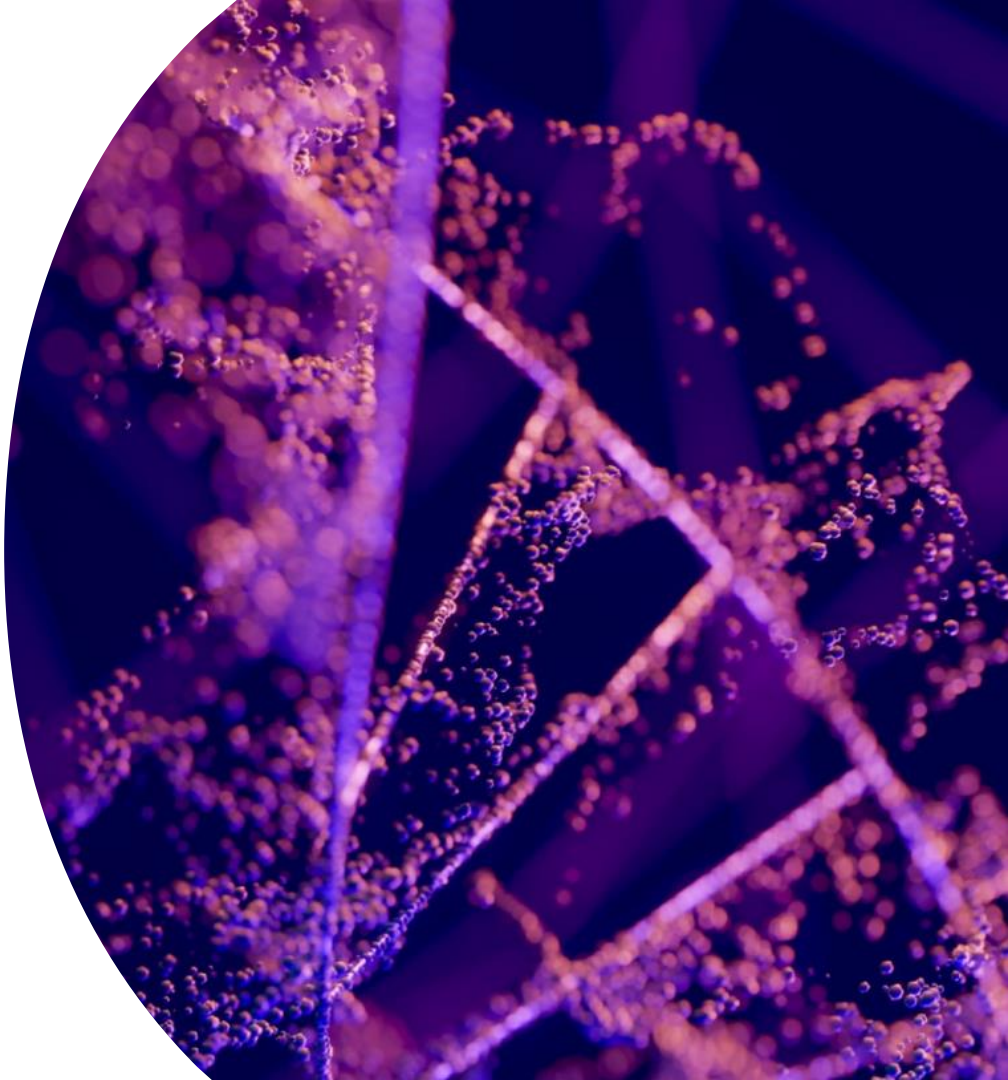
Tom Snow
Global Franchise Head, Neurology

Erik Wallstroem, MD PhD
Therapeutic Area Head, Multiple Sclerosis

Anthony Traboulsee, MD
Professor and Research Chair of the MS Society of Canada at the University of British Columbia, Vancouver

Tim Turner, PhD
Global Project Head, Neurology

Appendix



ALS Study Population

Inclusion criteria

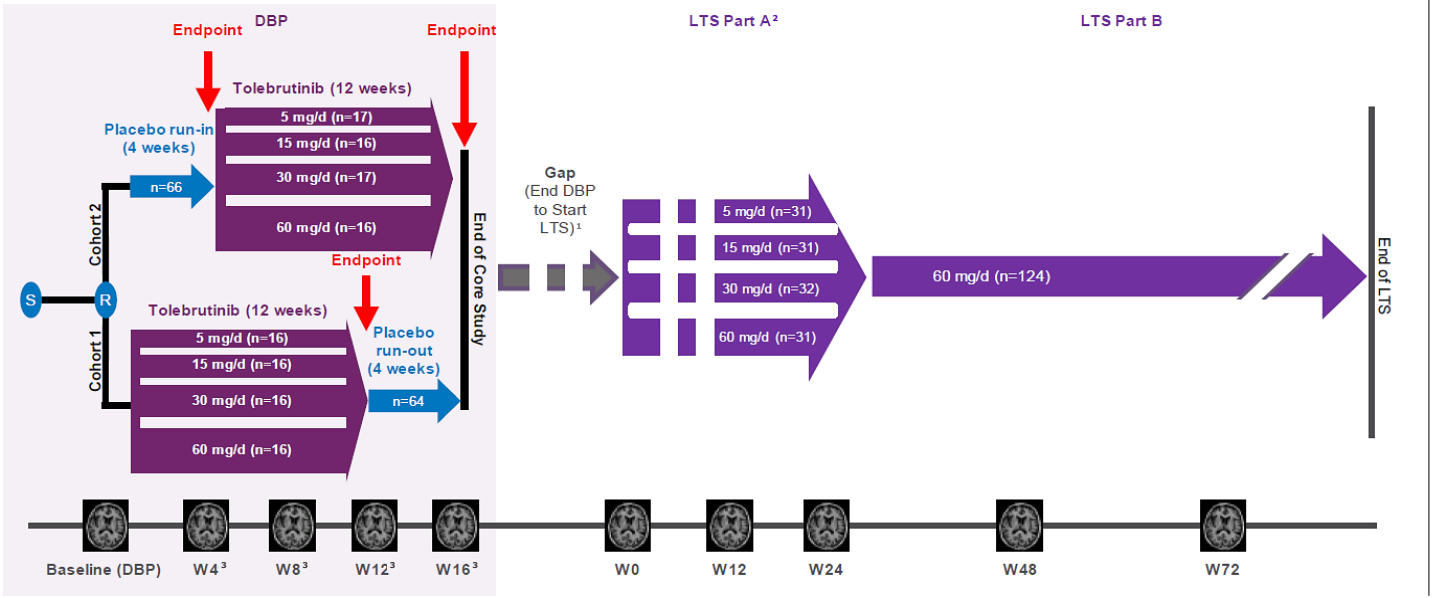
- Age 18 - 80 years
- Diagnosis of possible, clinically probable ALS, clinically probable laboratory-supported ALS, or clinically definite ALS
- ALS disease duration ≤ 2 years (from first symptom onset to the screening visit)
- SVC ≥60% of predicted value
- Able to swallow study tablets at the screening visit
- Either not currently receiving riluzole/edaravone or on a stable dose

Exclusion criteria

- Currently taking moderate/strong CYP3A4 inhibitors or strong CYP3A4 inducers
- History of seizures
- Cognitive impairment
- Currently participating in other interventional trials or taking any investigational treatment

ALS: Amyotrophic Lateral Sclerosis; CYP3A4: Cytochrome P450 3A4; SVC: Slow Vital Capacity.

Ph2b LTS study design



(1) Gap period in the transition between last dose in the DBP and first dose in the LTS study was variable (mean ± SD, 7 ± 7.3 weeks; range, 0-21 weeks). (2) Duration of Part A of the LTS study was variable (mean ± SD, 27.4 ± 6.3 weeks; range, 15-47 weeks). (3) DBP MRI scans in this figure are labelled according to the week of the DBP; in contrast, the DBP time points in Figure 2 and 3 indicate the number of weeks on tolebrutinib treatment in the DBP.
DBP: Double-Blind Period; LTS: Long-Term Safety; R: Randomization; S: Screening; W: Week.
Tolebrutinib is an investigational agent that has not been reviewed by any regulatory agency worldwide.