Roche Pharma Day 2020

Late Stage Pipeline Neuroscience

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Neuroscience and rare diseases portfolio

Strongly differentiated pipeline

Phase 1 (5 NMEs)

RG6102	**brain shuttle gantenerumab** Alzheimer's
RG7816	**$GABA_A$ α5 PAM** Autism spectrum disorder
RG7637	undisclosed
RG6091	**UBE3A-LNA** Angelman syndrome RD
RG6237	undisclosed

Phase 2 (3 NMEs)

RG7935	**prasinezumab** Parkinson's
RG6100	**semorinemab (anti-Tau)** Alzheimer's
RG7906	**ralmitaront** Schizophrenia

Late Stage (4 NMEs)

RG1450	**gantenerumab** Alzheimer's
RG6042	**tominersen** Huntington's RD
SRP 9001	**microdystrophin gene therapy** DMD RD
RG7845	**fenebrutinib** MS

Launched (3)

RG1594	**Ocrevus** MS	
RG7916	**Enspryng (satralizumab)** NMOSD RD	✓
RG7916	**Evrysdi (risdiplam)** SMA type 1/2/3 RD	✓

✓ FDA approval in 2020

RD RD=Rare Diseases

Neuro-immunologic disorders | Neuro-degenerative disorders | Neuro-developmental disorders | Neuro-muscular disorders | Psychiatric disorders

Risdiplam is developed in collaboration with PTC therapeutics and the SMA Foundation; Tominersen (ASO HTT) is developed in collaboration with Ionis Pharmaceuticals; ALS=Amyotrophic lateral sclerosis; NMOSD=neuromyelitis optica spectrum disorders; DMD=Duchenne muscular dystrophy; MS=Multiple sclerosis

Late stage pipeline update

1. **Hematology franchise**
   - DLBCL: Polivy, glofitamab, mosunetuzumab
   - FL: mosunetuzumab, glofitamab, Polivy
   - AML: Venclexta
   - MM: Venclexta
   - MDS: Venclexta

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   - KRAS *G12C*+: GDC-6063

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   - Influenza A/B: Xofluza
   - SARS-CoV2: Actemra
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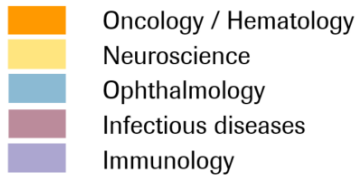


* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 20 results presentation appendix or visit the IR homepage

MS franchise: Ocrevus shifting the standard of care

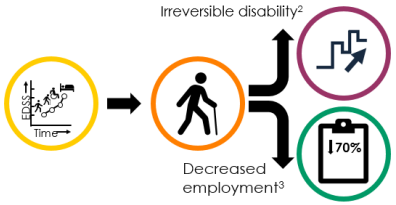
Robust, consistent, sustained impact on slowing disability progression

OCREVUS® ocrelizumab

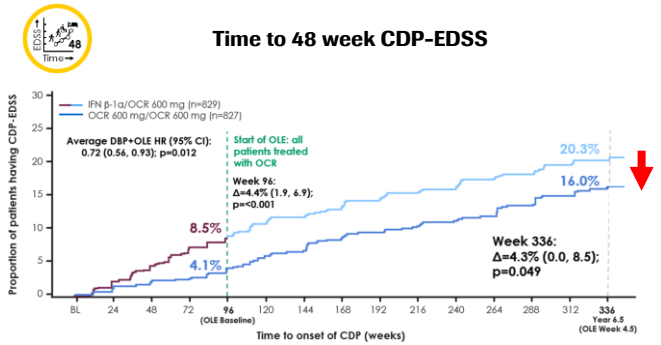
Roche

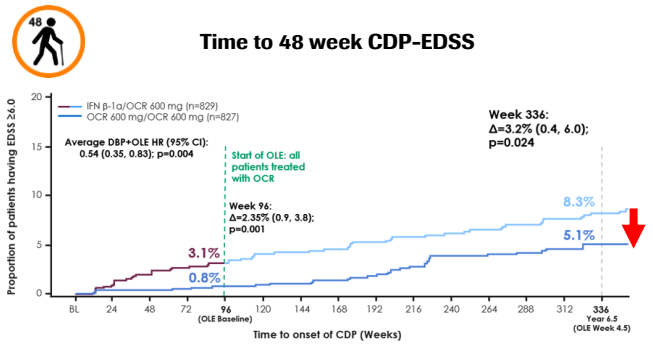
MS VIRTUAL 2020 ACTRIMS-ECTRIMS MEETING SEPTEMBER 11-13

RMS: Ph III (OPERA) 6.5-year follow-up



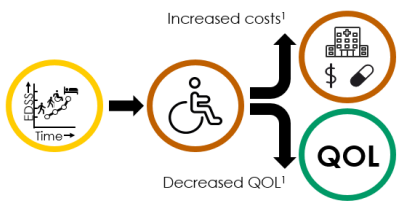
Reaching EDSS score ≥6.0, a key clinical disability milestone representing the requirement of a walking aid, which is associated with increased patient and societal burden



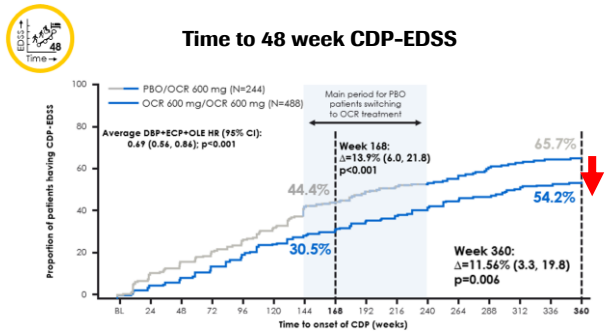


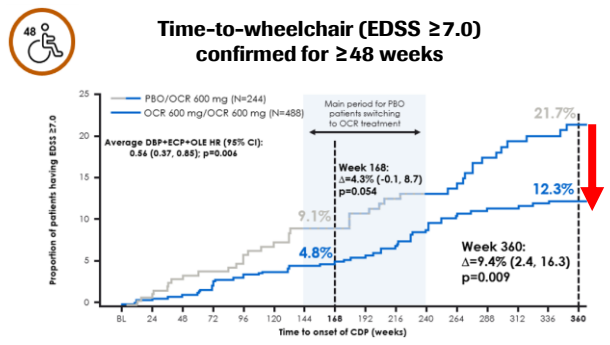
RMS patients on Ocrevus over 6.5 yrs had a 46% reduction in the risk of needing a walking aid vs those who switched over from IFN β-1α treatment at the end of the double-blind period (p=0.004)

PPMS: Ph III (ORATORIO) 7-year follow-up



Reaching EDSS score ≥7.0, a key clinical disability milestone representing wheelchair confinement, has a major impact on patients' quality of life and associated treatment costs[1]





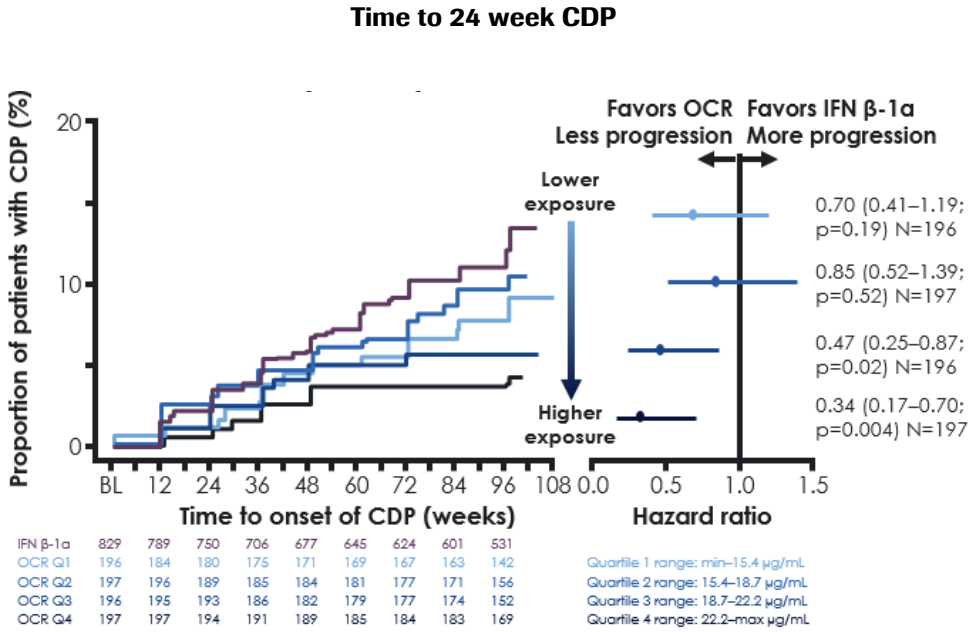
PPMS patients on Ocrevus over 7 yrs had a 44% reduction in the risk of needing a wheelchair (EDSS) vs those who switched over from IFN β-1α treatment at the end of the double-blind period (p=0.006)

Giovannoni G. et al, ACTRIMS-ECTRIMS 2020; Wolinsky J.S. et al, ACTRIMS-ECTRIMS 2020; 1. Kobelt G, *et al. Mult Scler* 2017;23:1123–1136; 2. Tomassini V, *et al. MSJ* 2019;25:1306–1315; 3. Kobelt G, *et al. MSJ* 2017;23:1123–1136 IFN=interferon; OCR=Ocrevus; RMS=relapsing multiple sclerosis; 24W-CDP=24 week-confirmed disability progression

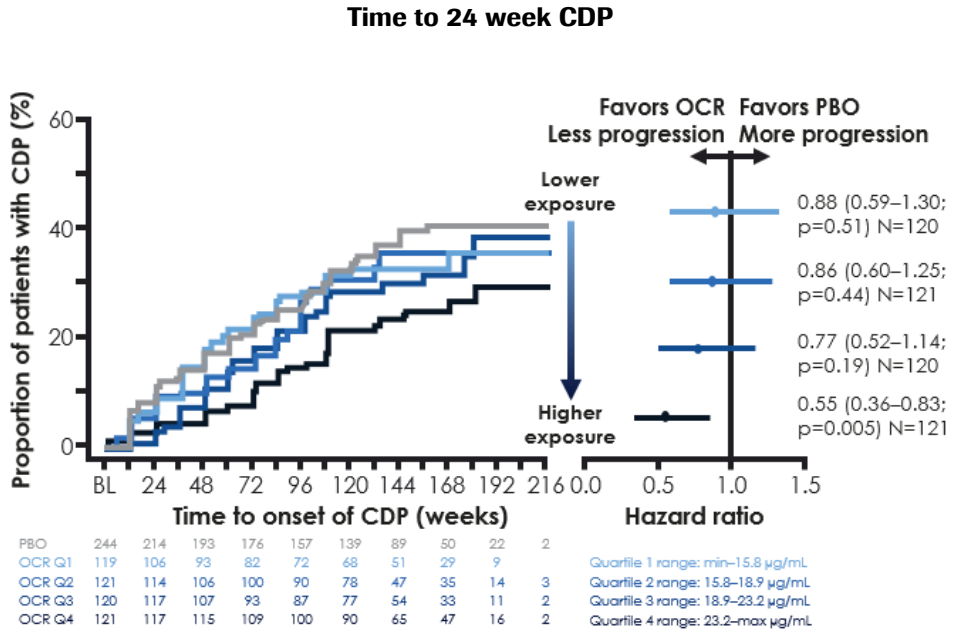
MS franchise: Scientific rationale for higher dose Ocrevus

Higher Ocrevus exposure reduces risk of disability progression

Exposure-response analysis in RMS



Exposure-response analysis in PPMS



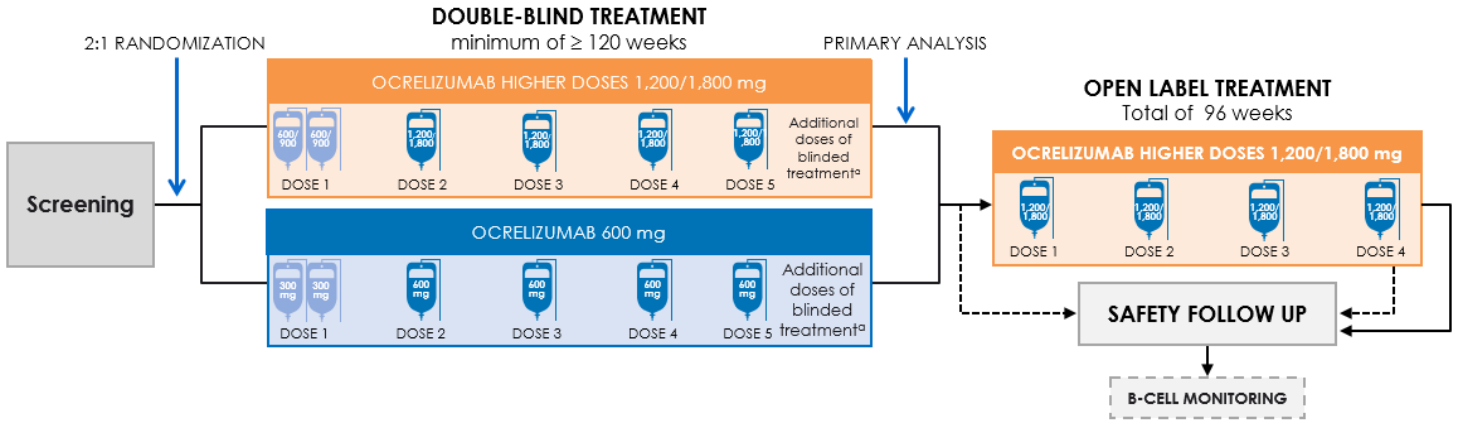
- Higher Ocrevus exposure was associated with lower B-cell levels and with greater control of disability progression without impacting safety

Hauser S.L. et al, ACTRIMS-ECTRIMS 2020; 24W-CDP=24 week confirmed disability progression; IFN=interferon; OCR=Ocrevus; PBO=placebo; RMS=relapsing multiple sclerosis; PPMS=primary progressive MS; Q=quartile

MS franchise: Higher dose Ocrevus

New Ph III program in RMS and PPMS planned to start in 2020

Ph III study design for Ocrevus higher dose versus 600 mg in RMS and PPMS



Study in patients with RMS (MUSETTE)

- Patient sample size, N=786
- Age: 18–55 years; EDSS score: 0–5.5
- Stratification for region, age, EDSS, weight

Study in patients with PPMS (GAVOTTE)

- Patient sample size, N=699
- Age: 18-55 years; EDSS score: 3–6.5
- Stratification for region, age, sex, weight

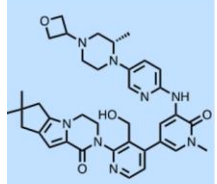
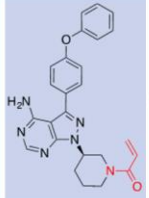
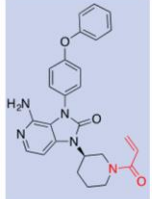
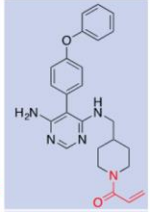
- Ocrevus showed a significant benefit on 12/24W-CDP, ARR, MRI measures in Ph III studies in RMS and PPMS and 7 year OLE
- Exposure/response analysis suggests a higher dose could further lower the risk of disability progression without compromising safety
- Two double-blind, randomized Ph III studies designed to test higher dose Ocrevus; selected higher dose, given every 24 weeks, is 1,200 mg for patients <75 kg or 1,800 mg for patients ≥75 kg
- Ph III (MUSETTE) in RMS and Ph III (GAVOTTE) in PPMS to start in 2020

Hauser S.L. et al, ACTRIMS-ECTRIMS 2020; 24W-CDP=24 week confirmed disability progression; AAR=annual relapse rate; MRI=magnetic resonance imaging; RMS=relapsing multiple sclerosis; PPMS=primary progressive MS; OLE=open label extension

MS franchise: Fenebrutinib in MS

Highly differentiated and potentially best-in-class BTKi in MS

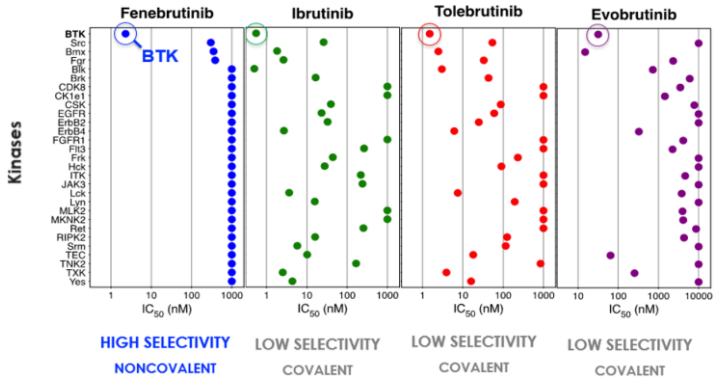
BTK inhibitor

Fenebrutinib (GDC-0853)	Ibrutinib	Tolebrutinib	Evobrutinib
Phase 3	Launched	Phase 3	Phase 3
MS	Oncology	MS	MS
			
Noncovalent, reversible	Covalent, irreversible	Covalent, irreversible	Covalent, irreversible
BTK IC_{50} 2 nM	1 nM	1 nM	32 nM
High selectivity	Low selectivity	Low selectivity	Low selectivity

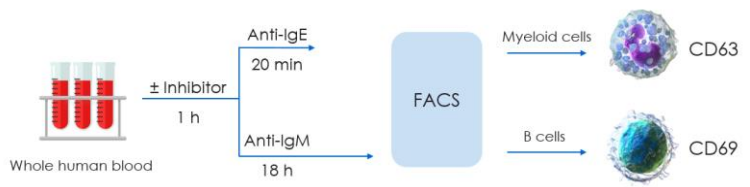
- Oral, highly selective and only reversible noncovalent BTK inhibitor
- Long residence time bound to BTK mimics the durable inhibition of a covalent inhibitor but without the safety risks of covalent BTK inhibition

Molecular and biological characterization

Kinase selectivity assay



B cell and myeloid cell activation assay



Whole human blood assay	Fenebrutinib[1]	Ibrutinib[1]	Tolebrutinib[2]	Evobrutinib[3]
Myeloid cell CD63 IC_{50}, nM	31	171	166	1660
B cell CD69 IC_{50}, nM	8	12	10	84

- Fenebrutinib's BTK inhibition potential and kinase selectivity were assessed in a panel of 219 human kinases. fenebrutinib was found to be highly BTK selective over other kinases which may reduce off target effects and improve safety
- Dual MOA: Fenebrutinib was shown to potently inhibit B cell and myeloid cell (macrophages, microglia) activation in whole human blood and thus may reduce both acute and chronic inflammation in MS, simultaneously

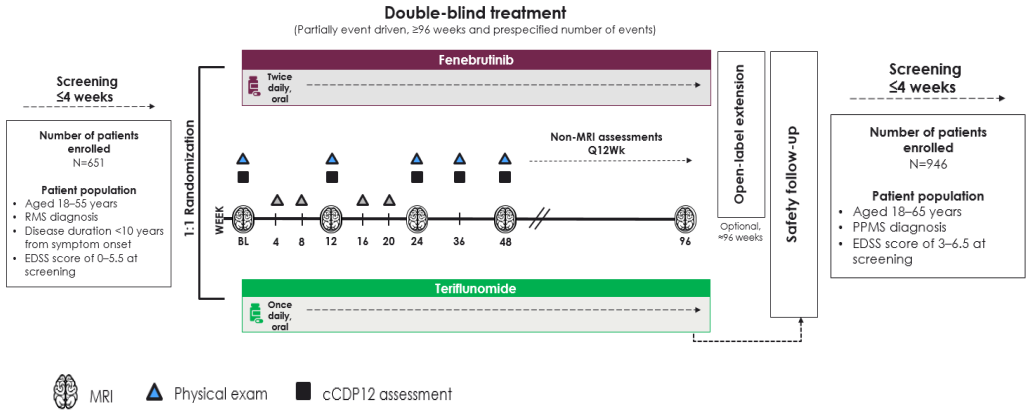
Johnson A. et al, ACTRIMS-ECTRIMS 2020; MS=multiple sclerosis; BTK=Bruton's tyrosine kinase; nM=nano molar; FACS=fluorescence-activated cell sorting

MS franchise: Fenebrutinib in MS

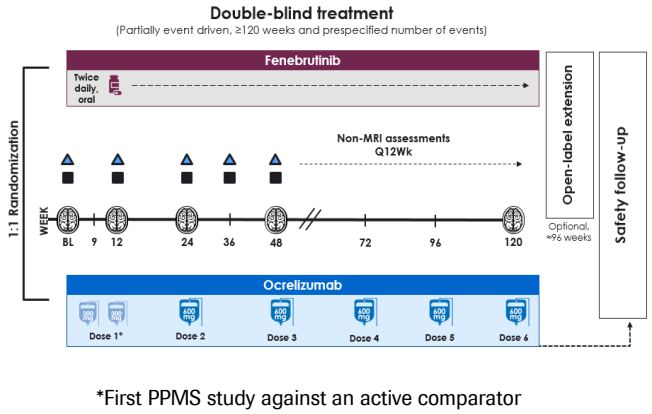
Ph III program to assess disease progression in RMS and PPMS

Ph III trial designs

Ph III RMS (FENhance)



Ph III PPMS (FENtrepid)*



*First PPMS study against an active comparator

Primary endpoint

cCDP12

≥12 weeks after the initial disability progression, confirmation of ≥1 of the following:

confirmed disability progression on **Expanded Disability Status Scale (EDSS)**[a]

or

≥20% increase from baseline in **9-Hole Peg Test**

or

≥20% increase from baseline in **Timed 25-Foot Walk Test**

- Fenebrutinib has a well established safety profile due to 13 clinical studies with >1200 patients, thereof 535 patients exposed for >1year; generally well tolerated, mostly non-serious, mild and self-limiting AEs
- Primary endpoint is composite Confirmed Disability Progression 12 (cCDP12); co-primary endpoint in RMS is ARR
- cCDP12 provides a more thorough approach to disability progression, including EDSS (global assessment scale), 9HPT (hand function) and T25FWT (ambulation ability). cCDP12 assesses upper limb function and may detect disease progression earlier
- Ph III program in RMS and PPMS to start enrollment in 2020

Hauser S. L. et al, ACTRIMS-ECTRIMS 2020; MS=multiple sclerosis; RMS=relapsing MS; PPMS=primary progressive MS; BL=base line; Q12W=every 12 weeks; [a] Defined as an increase of ≥1 point from a baseline score of ≤5.5, or an increase of ≥0.5 points from a baseline score of >5.5; EDSS=Expanded Disability Status Scale; 9HPT=9-Hole Peg Test; T25FWT=Timed 25-Foot Walk Test; AE=adverse event

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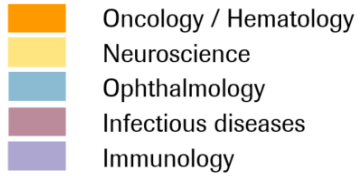

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SMA franchise: Evrysdi in type 1/2/3 SMA

Compelling benefit/risk profile in infants, children, adults

Evrysdi risdiplam

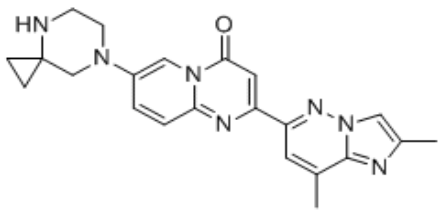
Roche

AAN 2020 Annual Meeting

FDA approved

SMN2 splicing modifier

EMA PRIME



- Efficacy in infants, children, adults
- Durably increases SMN protein throughout the CNS and in peripheral tissues
- Consistent safety profile in over 450 risdiplam-treated patients in trials
- First and only at-home treatment

FIREFISH part 2 results in type 1 SMA confirm highly competitive profile

The primary endpoint was met (P<0.0001)*

29%
(12/41)

of infants were sitting without support for 5 seconds at Month 12, as measured by the BSID-III

Risdiplam treatment led to a significant improvement in motor function† (P<0.0001)‡

Infants achieved motor milestones, such as sitting and standing§ that would never be seen in untreated infants

93%
(38/41)
of infants were alive and

85%
(35/41)
of infants were event free‖ at Month 12

95%
(36/38)
of infants alive maintained the ability to swallow after 12 months of treatment

49%
(20/41)
of all infants did not require hospitalization¶ during 12 months of treatment

No drug-related safety findings led to withdrawal in FIREFISH Part 2

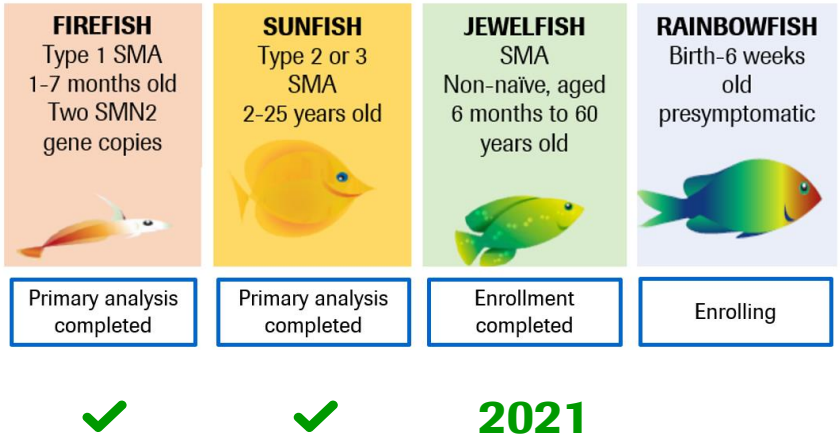
- Positive Ph III (FIREFISH part 2) in older, symptomatic type 1 infants
- Positive Ph III (SUNFISH part 2) the only placebo controlled study in a broad spectrum of type 2/3 patients (age 2-25)
- US approval achieved in Q3 2020; filed in EU, Brazil, Canada, China and 14 further countries

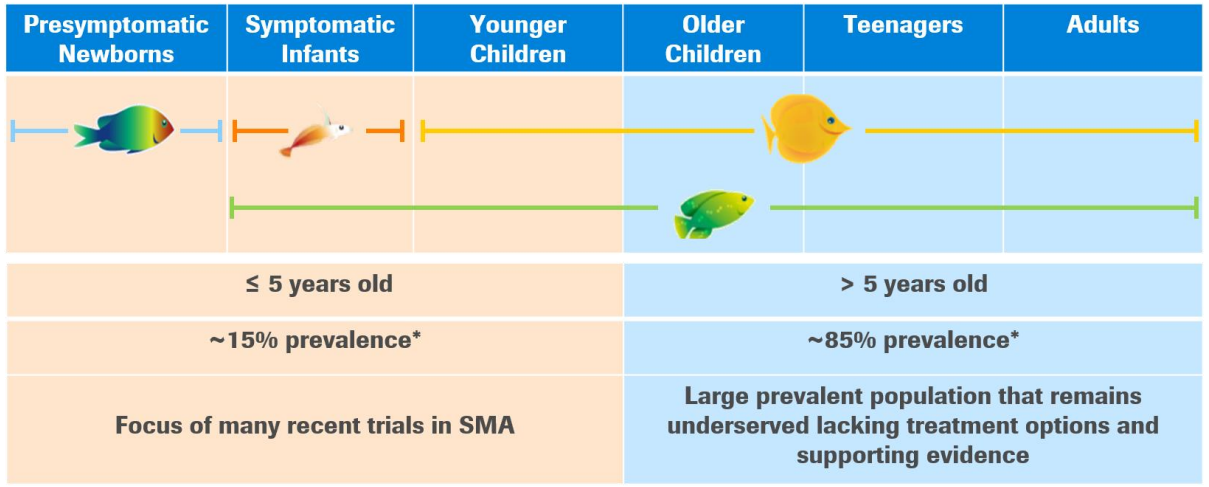
Servait L.. et al. AAN 2020; *Performance criterion=5%, exact binomial test. †As measured by CHOP-INTEND. ‡Performance criterion=12%, exact binomial test. §As measured by HINE-2; ‖Event-free in FIREFISH is defined as alive with no permanent ventilation (i.e. no tracheostomy or BiPAP ≥16 hours per day continuously for >3 weeks or continuous intubation >3 weeks, in the absence of, or following the resolution of, an acute reversible event). ¶Hospitalizations include hospital admissions ≥1 night; BiPAP, Bilevel Positive Airway Pressure; BSID-III, Bayley Scales of Infant and Toddler Development, Third edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2.; Risdiplam in collaboration with PTC Therapeutics and the SMA Foundation

SMA franchise: Evrysdi in type 1/2/3 SMA

Additional data for switching patients and newborns

Broadest Ph III program in SMA on-going





- Ph III (JEWELFISH) switching study fully recruited (n=174); Prior treatments were olesoxime (n=74), Spinraza (n=73), Zolgensa (n=14); RG7800 (n=13); JEWELFISH exploratory efficacy to be reported after 1 year of follow-up in 2021
- Ph III (RAINBOWFISH) presymptomatic study enrollment on-going
- Evrysdi has the potential to become the treatment of choice for the majority of SMA patients as our broad clinical trial program covers the broad, real-world spectrum of people living with SMA – including under-served and under-represented patient populations

Risdiplam in collaboration with PTC Therapeutics and the SMA Foundation; * Estimated 2020 prevalence in US and EU5

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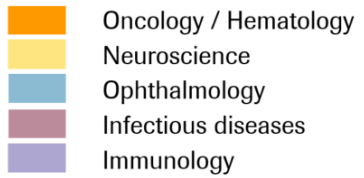
   - SARS-CoV2: Actemra
   - SARS-CoV2: REGN-COV2



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Enspryng in NMOSD

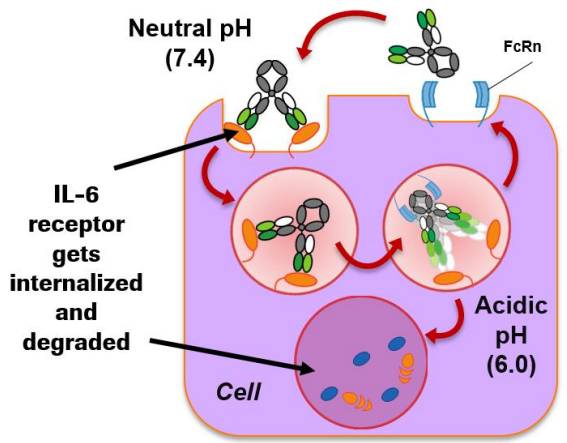
Significantly reduced frequency and severity of relapses

ENSPRYNG satralizumab-mwge subcutaneous injection 120 mg/mL

Roche

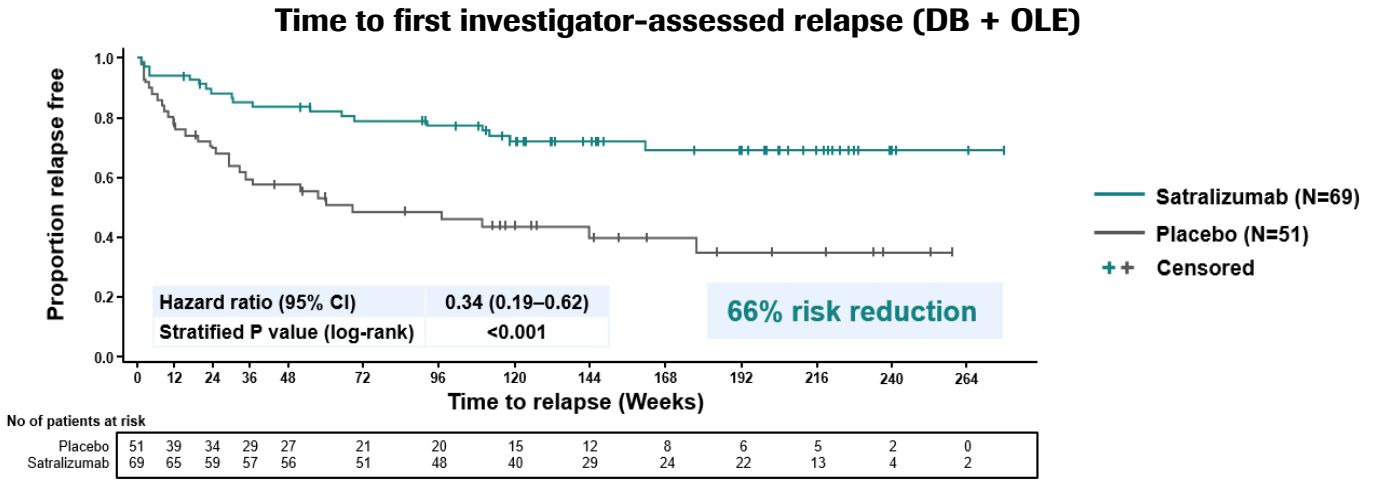
MS VIRTUAL 2020 ACTRIMS-ECTRIMS MEETING SEPTEMBER 11-13

Anti-IL-6 receptor mAb



- Recycling mAb with high-affinity to soluble and membrane-bound IL-6R
- Engineered to enable maximal inhibition of IL-6 signalling
- Convenient SC Q4W dosing at home

Ph III (SAkura) up to 5 year follow-up (AQP4+ patients)



- Continued risk reduction of relapse for up to 5 years; AQP4+ patients experiencing a 66% risk reduction, and all patients experiencing a 51% risk reduction vs those originally randomized to placebo; treatment associated with a significant reduction in severe relapses vs placebo
- Pooled longer-term data from the SAkura studies show a continued favorable safety profile
- Roche is actively exploring Enspryng in other rare indications where IL-6 is implicated

Greenberg B, et al. ACTRIMS-ECTRIMS Meeting (MSVirtual2020); Palace J, et al. ACTRIMS-ECTRIMS Meeting (MSVirtual2020); Greenberg B, et al. ACTRIMS-ECTRIMS Meeting (MSVirtual2020); NMOSD=neuromyelitis optica spectrum disorder; AQP4=aquaporin-4; DB+OLE=double-blind and open-label extension

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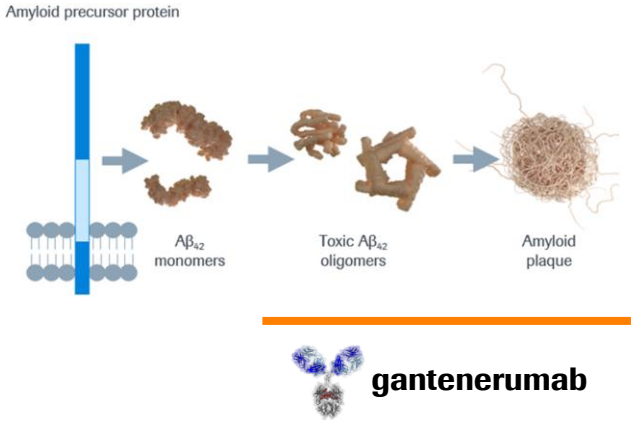
AD: Gantenerumab targeting Amyloid β (Aβ)

Strong target engagement and downstream biological impact

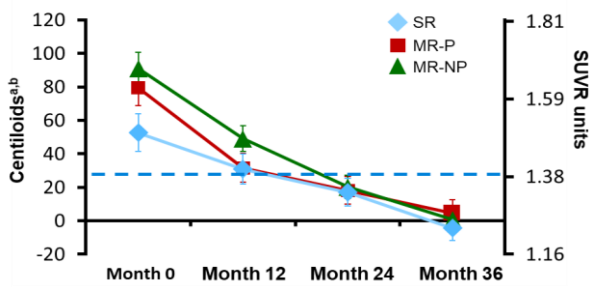
Anti-Aβ mAb



- Fully human, anti-Aβ mAb (IgG1) with high affinity to aggregated forms of Aβ
- Highest affinity for neurotoxic oligomers and plaques [1,2]
- SC administration enables flexibility of home administration

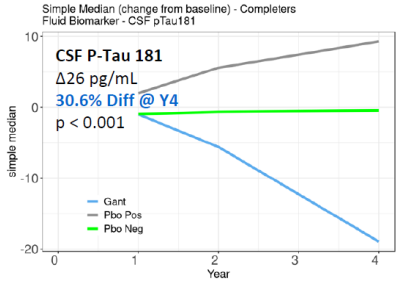
OLE shows robust Aβ removal*

Aβ levels over 3 years

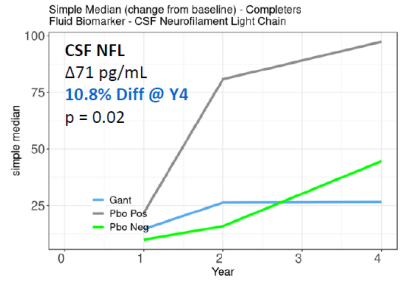


DIAN-TU shows downstream impact

CSF Phospho-Tau levels over 4 years



CSF NfL levels over 4 years



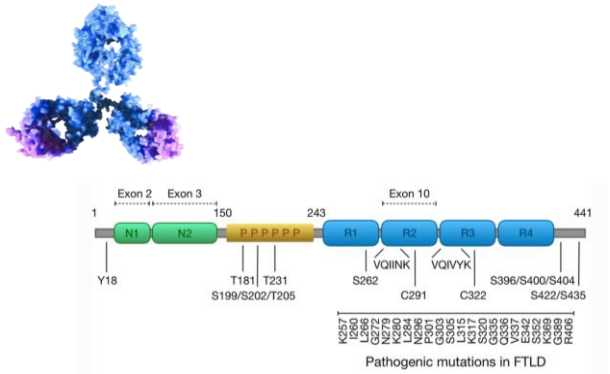
- Gantenerumab lowers Aβ below positivity threshold towards floor levels without plateau; at 3 years 80% of patients were Aβ-negative in OLE studies
- Gantenerumab reduces levels of downstream biomarkers (phosphorylated Tau) and blocks increases of markers of neurodegeneration (NfL) in patients with familial AD (DIAN-TU study)
- Ph III (GRADUATE 1/2) program with optimized exposure by dose (single dosing scheme) and duration (27 months of treatment) on-going; results expected in 2022

1. Bohrmann B, et al. J Alzheimer's Dis 2012; 2. Ostrowitzki S, et al. Arch Neurol 2012; Bateman R. J. et al, AAT-AD/PD 2020; Klein G et al, CTAD 2020; OLE=open label extension; NfL=neurofilament light chain; SC=subcutaneous; * OLE studies for the former Ph III studies SCarlet RoAD and Marguerite RoAD

AD: Semorinemab targeting anti-Tau

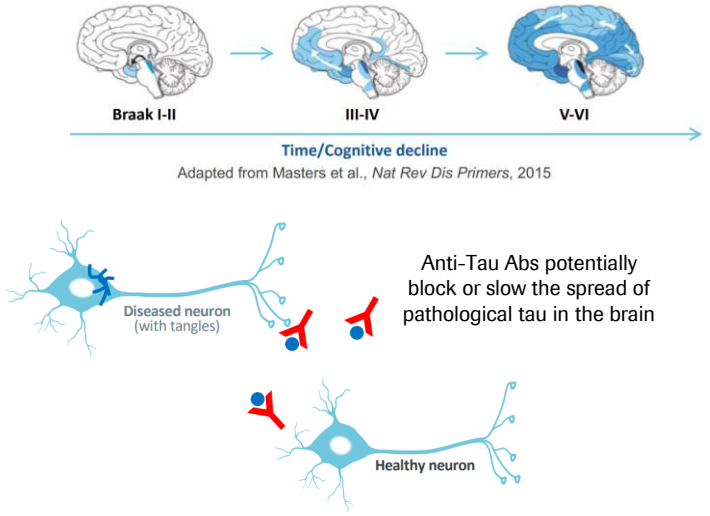
Ph II (TAURIEL) results for semorinemab expected in H2 2020

Anti-Tau mAb



- First-in-class humanized Ab
- Recognizes N-terminal epitope
- Targets all known isoforms of full length Tau independent of their phosphorylation status

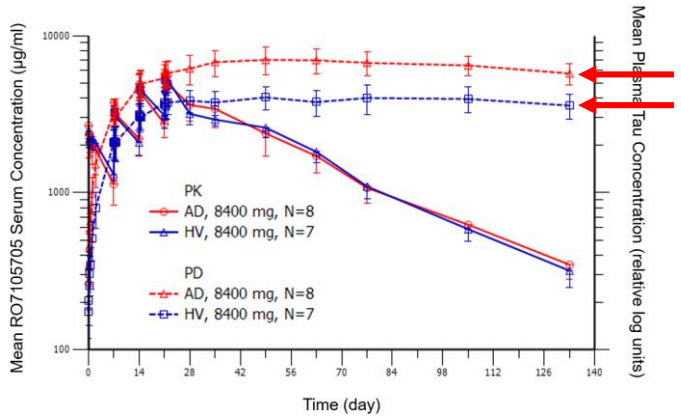
Proposed MOA



- No AEs associated with semorinemab in pre-clinical studies; safe and well tolerated in Ph I
- Robust biomarker development with two tau PET tracers in development
- Results from blinded portion of Ph II (TAURIEL) in prodromal-to-mild AD expected in H2 2020; primary endpoint includes CDR-SB; secondary endpoints include cognitive tests (ADAS-Cog13, RBANS Total Score) and functional tests (ADCS-ADL, Amsterdam iADL)
- Second Ph II (LAURIET) in patients with moderate AD on-going

Ph I (PK/PD) results

Plasma Tau conc in AD patients 2x higher than in HV after semorinemab administration

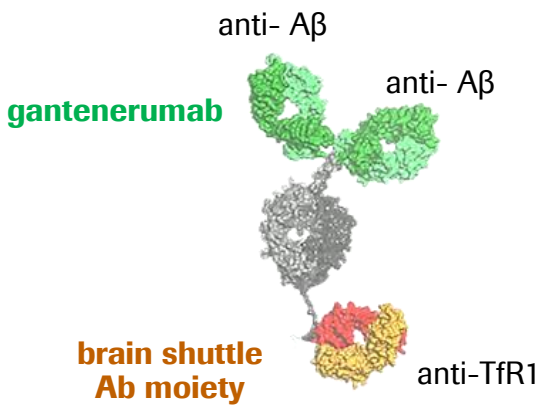


Teng E. et al. CTAD 2019; Kerchner et al. CTAD 2017; PD=pharmacodynamics; PK=pharmacokinetics; HV=healthy volunteer; AD=Alzheimer's disease; ADAS-Cog=Alzheimer's Disease Assessment Scale–Cognitive subscale; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory; Amsterdam iADL=Amsterdam Instrumental Activities of Daily Living scale; CDR-SB=Clinical Dementia Rating–Sum of Boxes; RBANS=Repeatable Battery for the Assessment of Neuropsychological Status; Semorinemab partnered with AC Immune; PET=positron emission tomography

AD: Gantenerumab brain shuttle (RG 6102)

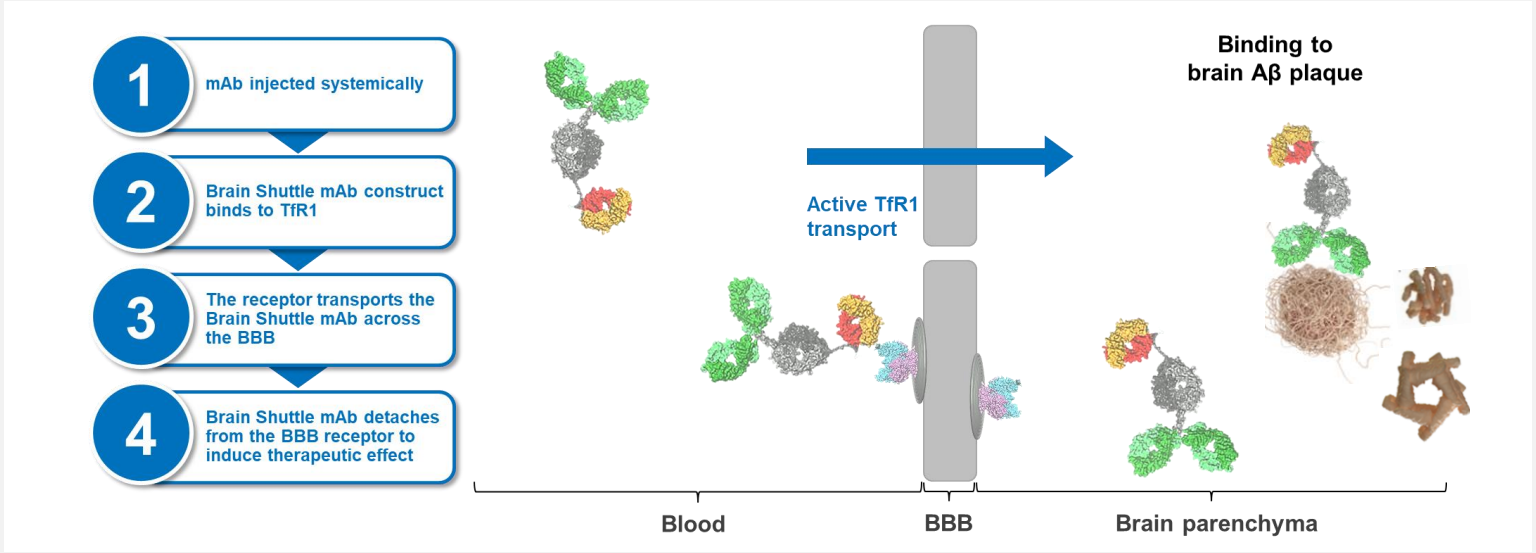
Vision: Superior target access leading to slowing of AD progression

Anti-Aβ-TfR1 fusion protein



- Gantenerumab with a novel transferrin receptor (TfR1) binding Ab moiety to achieve efficient transport over the BBB and target Aβ engagement in the brain
- Technology could also be applied to other CNS disorders

MOA: Superior brain access through brain shuttle technology



- Preclinical work provides in vitro and in vivo evidence that binding to the TfR1 receptor facilitates transcellular transport across the Blood Brain Barrier (BBB)
- The first brain shuttle mAb entered the clinic in 2019
- Preliminary Ph I PK/PD data are currently under evaluation to determine next steps

1. Niewoehner J, *et al. Neuron* 2014; 81:49–60; BBB=blood brain barrier; IgG=immunoglobulin G; mAb=monoclonal antibody; TfR1=transferrin receptor 1; Aβ=Amyloid β; CNS=central nervous system; PD=pharmacodynamics; PK=pharmacokinetics

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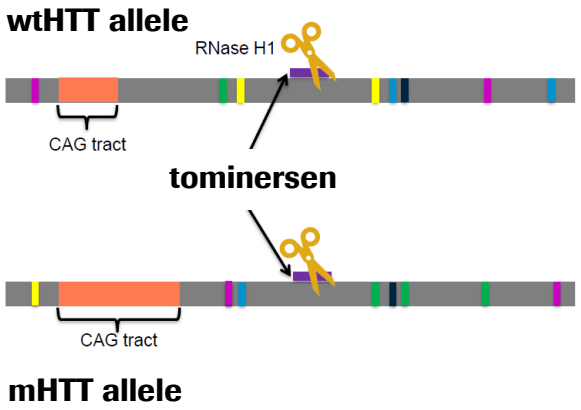
Tominersen (HTT-ASO) in Huntington's disease

First drug to reduce toxic mHTT

Antisense RNA

EMA PRIME

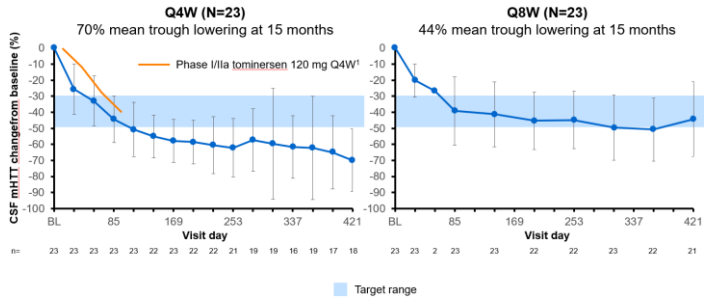


- Antisense drug binds to wtHTT and mHTT sequence leading to RNase H1 mediated degradation of wild-type and mutant HTT mRNA
- Addresses all patients

Ph II update

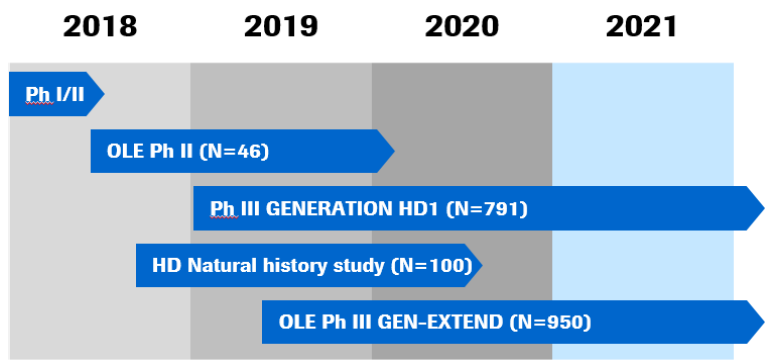
CHDI FOUNDATION February 24-27

mHTT CSF levels from 15 month OLE cut



- Preliminary analysis of 15 month OLE data show sustained lowering of CSF mHTT exceeds or achieves target reduction range of 30-50% (Q4W; Q8W)
- Safe and well tolerated with no dose-limiting toxicities identified and no patients discontinuing
- Ph III (GENERATION HD1) enrollment completed in Q2 2020; results expected in 2022
- Data from the Ph I/II and Ph III OLE studies and the HD Natural History study expected in 2021

Ph III program



Schobel SA. et al, Cure Huntington's Disease Initiative - 15th Huntington's Disease Therapeutics Conference CHDI 2020; mHTT=mutant huntingtin; wtHTT=wild-type huntingtin; CSF=cerebrospinal fluid; OLE=open-label extension; Q4W=every 4 weeks; Q8W=every 2 months; IT=intrathecal; HTT-ASO licensed from IONIS Pharmaceuticals

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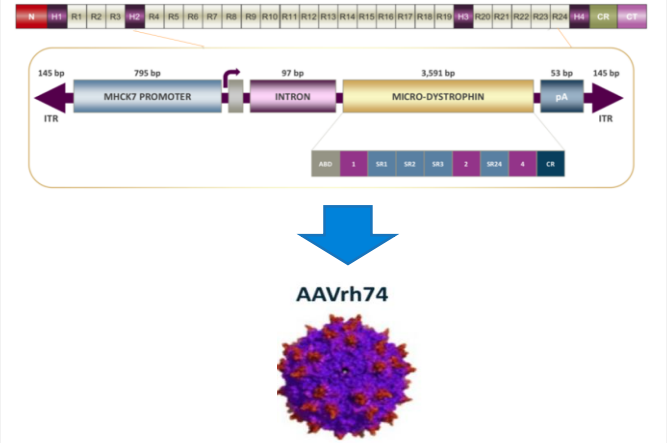
Micro-dystrophin Gene Therapy (SRP-9001) in DMD

Positive 1 year safety & efficacy data published in JAMA Neurology

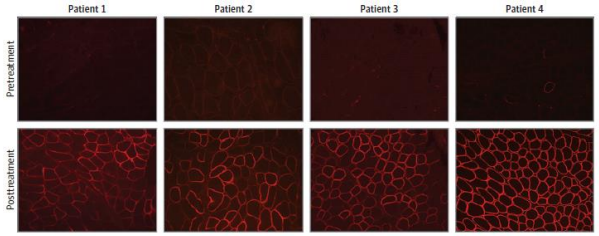
Micro-dystrophin gene therapy



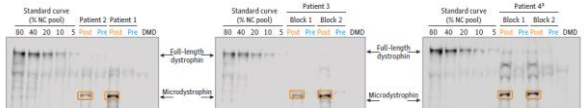
- AAVrh74 vector: low likelihood of pre-existing immunity and high tropism for skeletal & cardiac muscles
- Expression potentiated by the MHCK7 promoter in cardiac & skeletal muscles
- Transgene retains critical elements of dystrophin for a functional protein

Ph I/IIa open-label trial results (n=4)

Immunofluorescence staining



Western blot



North Star Ambulatory Assessment (NSAA)

Patient	Parameter	Baseline	Change from baseline at day 365
1	NSAA	18	7
	CK level, U/L	20 691	-46.48%
2	NSAA	19	8
	CK level, U/L	23 414	-55.18%
3	NSAA	26	2
	CK level, U/L	34 942	-81.66%
4	NSAA	19	5
	CK level, U/L	29 210	-85.75%

- 81.2% of muscle fibers expressing micro-dystrophin by immunohistochemistry with a mean intensity of 96% at the sarcolemma at 12-wks; adjusted for fat and fibrotic tissue Western blot showed a mean expression of 95.8%
- All patients showed improvements in NSAA score (mean, 5.5 points up to one year); therapy was well tolerated with minimal adverse events up to one year after treatment
- Planning for two global Ph III trials in ambulatory and non-ambulatory DMD patients are on-going

Mendell J. R. et al, JAMA Neurol. 2020 Jun 15; SRP-8011 partnered with Serepta; License and collaboration agreement with Sarepta Therapeutics in Duchenne Muscular Dystrophy (DMD), securing exclusive ex-US commercial rights to SRP-9001, their gene therapy for DMD, and the right to opt-in to their broader DMD portfolio outside of the US

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Prasinezumab in Parkinson's disease (PD)

Primary not met, but encouraging core PD motor signs

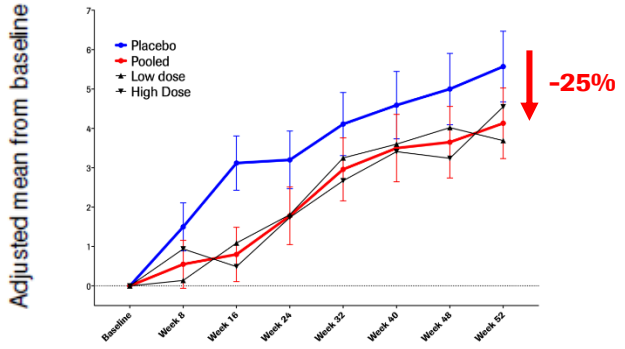
MDS Virtual Congress 2020
SEPTEMBER 12–SEPTEMBER 16

Anti-α-synuclein mAb

- Humanized mAb designed to target aggregated forms of α-synuclein
- Inhibiting cell-to-cell spreading of pathogenic forms of α-synuclein, resulting in slowing of PD progression

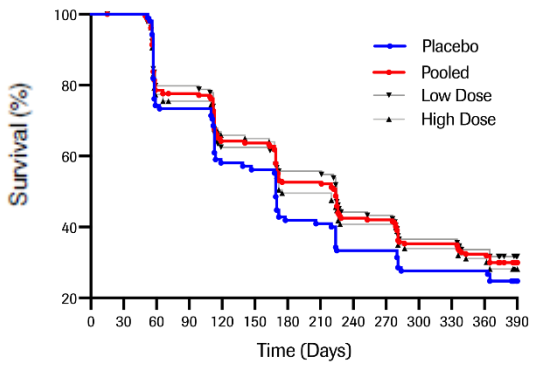
Ph II (PASADENA part 1) 52 weeks results

Change in MDS UPDRS part III



Pooled: −1.44, 80% CI=(-2.83, -0.06); **−25%**,
Low dose: −1.88, 80% CI=(-3.49, -0.27); **−34%**
High dose: −1.02, 80% CI= (-2.64, 0.61); **−18%**

Time to worsening of motor signs (+5pts MDS UPDRS part III)



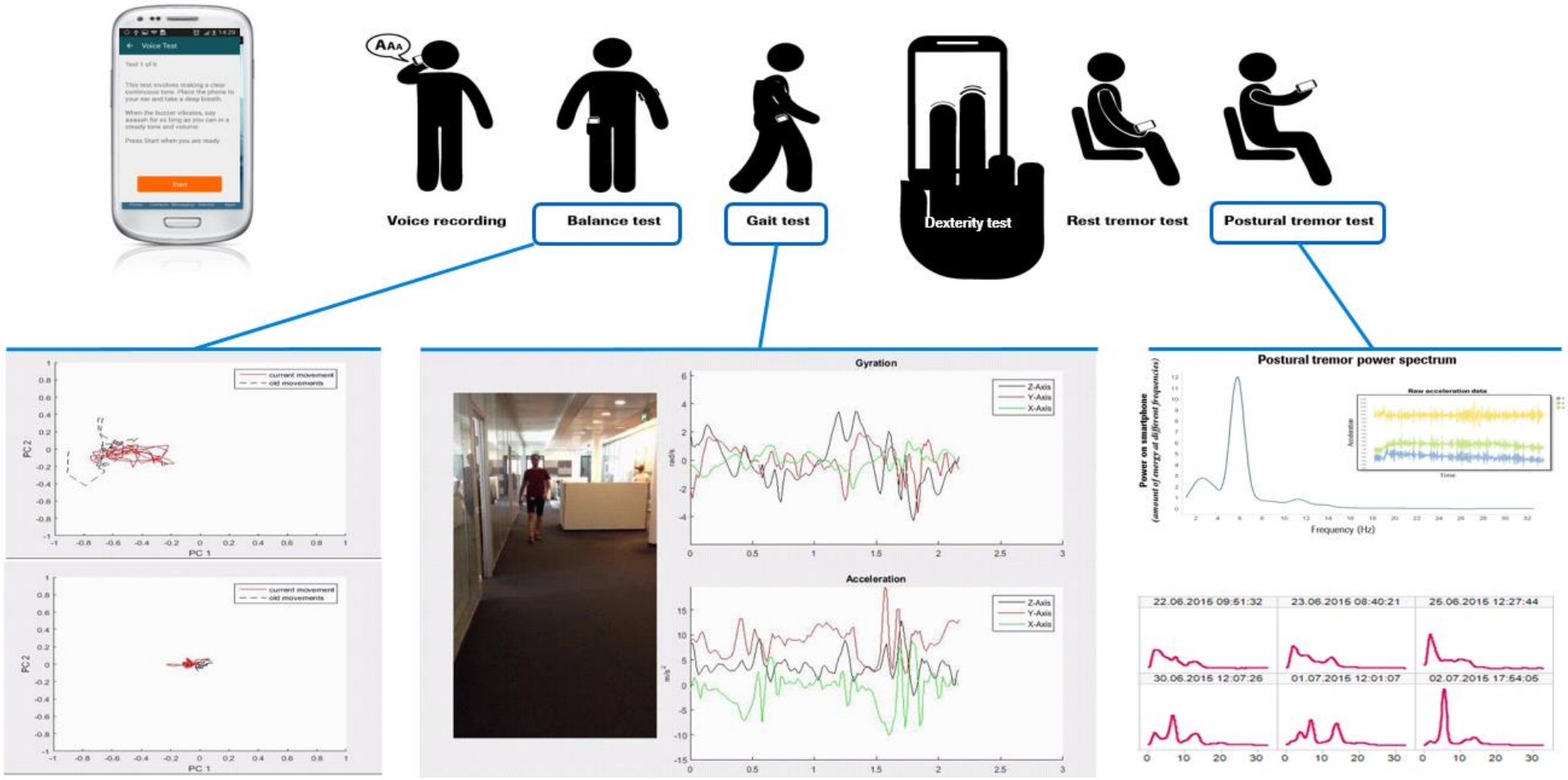
Pooled: HR 0.82, 80% CI=0.64 to 0.99
Low dose: HR 0.77, 80% CI=0.63 to 0.96
High dose: HR 0.87, 80% CI=0.70 to 1.07

- First Ph II (PASADENA) results were presented at MDS 2020 (poster session); additional results (including digital biomarker data) to be presented at the MDS presentation on Sep 15
- Study did not meet its primary endpoint (MDS UPDRS total score)
- Positive signals of efficacy on multiple pre-specified secondary assessments of motor function including motor signs (MDS UPDRS part III)
- Totality of data is being evaluated to determine next steps

Pagano, G et al, MDS poster 2020; MDS-UPDRS=Movement Disorder Society-Unified Parkinson's Disease Rating Scale (Sum of Parts I, II and III which assess non-motor [I and II] and motor [III] experiences in daily living); Prasinezumab partnered with Prothena Biosciences

Prasinezumab in Parkinson's disease

Digital biomarker active tests supporting clinical development



http://www.roche.com/media/store/roche_stories/roche-stories-2015-08-10.htm

Novel measurements & digital endpoints

Digital biomarkers - providing enhanced patient insights and novel endpoints

Apps, wearables and gaming devices

Digital biomarker program in neuroscience

Disease Area	Cognition	Hand Motor Function	Gait & balance	Vocalization	Activity & sociability
Parkinson	●	●	●	●	●
Huntington	●	●	●	●	●
SMA		●	●	●	
Multiple Sclerosis	●	●	●		●
Alzheimer	●			●	●
Autism	●			●	●
Schizophrenia					●

- Clinical trials utilizing mobiles, wearables and gaming devices
- More sensitive, precise and objective
- Continuous and longitudinal measurement captures episodic and rare events
- Reduced assessment burden and greater real-world relevance

Doing now what patients need next