Roche Pharma Day 2019

Late Stage Pipeline Neuroscience

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Neuroscience and rare diseases portfolio

Strongly differentiated pipeline

Phase 1 (3 NMEs)

RG7816	**$GABA_A$ α5 PAM** Autism spectrum disorder	
RG6000	ALS	RD
RG6237	undisclosed	

Phase 2 (4 NMEs)

RG7935	**prasinezumab** Parkinson's	
RG6100	**aTau** Alzheimer's	
RG1662	**basmisanil** CIAS	
RG7906	Schizophrenia	

Late Stage (6 NMEs)

RG1450	**gantenerumab** Alzheimer's		
RG7916	**satralizumab** NMOSD	RD	**2019**
RG7314	**balovaptan** Autism spectrum disorder		
RG7916	**risdiplam** Spinal muscular atrophy	RD	**2019**
RG6206	**anti-myostatin adnectin FP** DMD	RD	
RG6042	**ASO HTT** Huntington's	RD	

Launched

RG1594	**Ocrevus** MS	

2019 FDA filing

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; RG6042 (ASO HTT) is developed in collaboration with Ionis Pharmaceuticals; CIAS=Cognitive impairment associated with schizophrenia; ALS=Amyotrophic lateral sclerosis; NMOSD=neuromyelitis optica spectrum disorders; DMD=Duchenne muscular dystrophy; MS=Multiple sclerosis; FP=fusion protein

Late stage pipeline update

Topics covered in presentations and break-out sessions

1. **Hematology franchise**
   - CLL: Venclexta Gazyva
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   - Hemlibra

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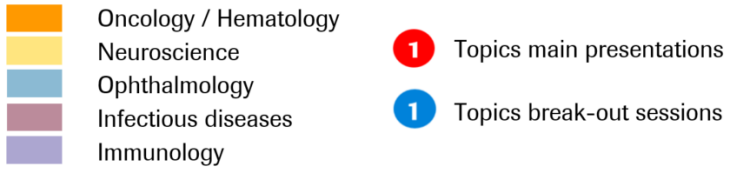
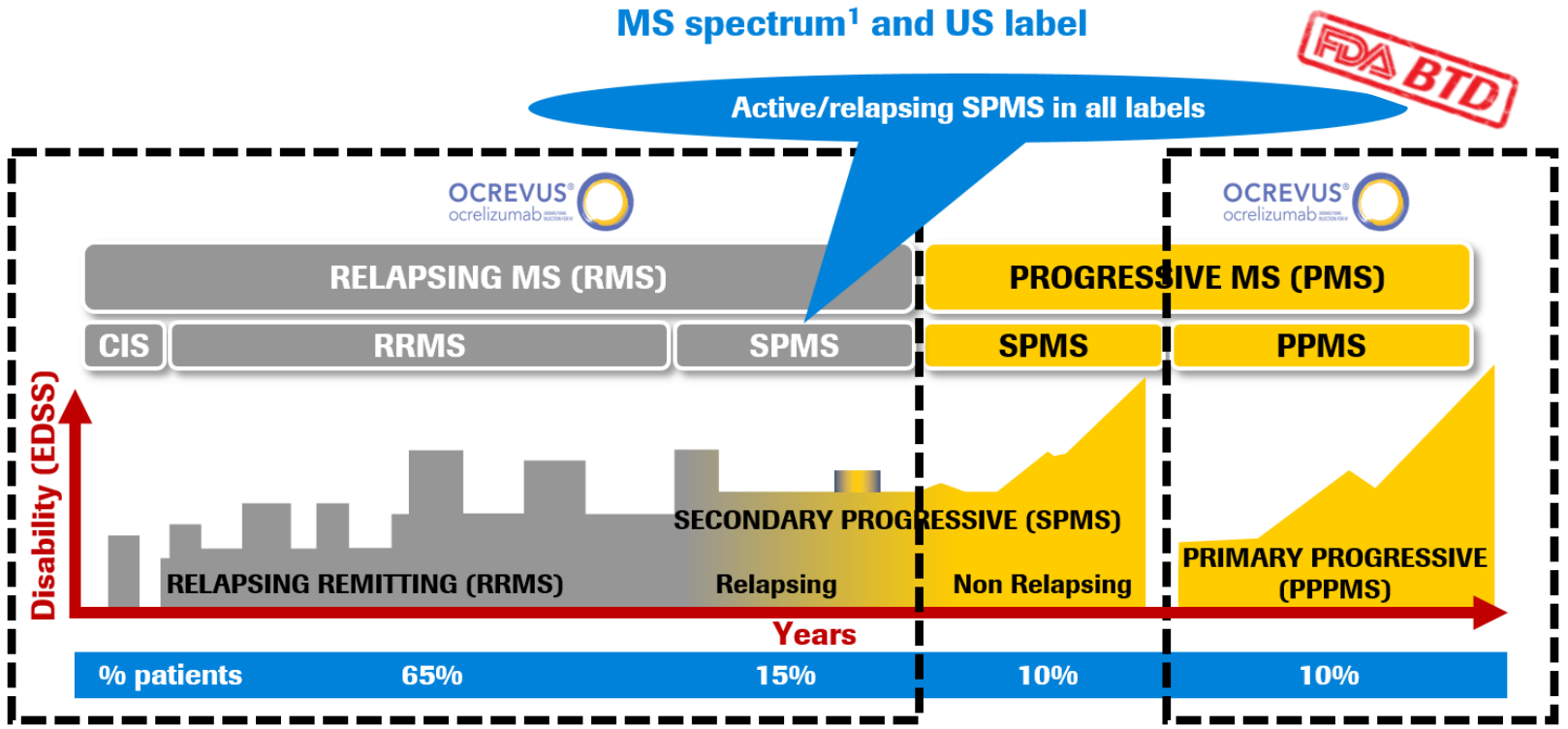


* For further information on target patient populations please consult the appendix; For further details on the late stage pipeline please consult the HY 18 results presentation appendix or visit the IR homepage

Neuroscience franchise: Ocrevus in MS

US label covers ~90% of MS patients including "active SPMS"&"CIS"

Now approved in 89 countries with over 120,000 patients treated globally. Convenient twice a year (every six month) dosing

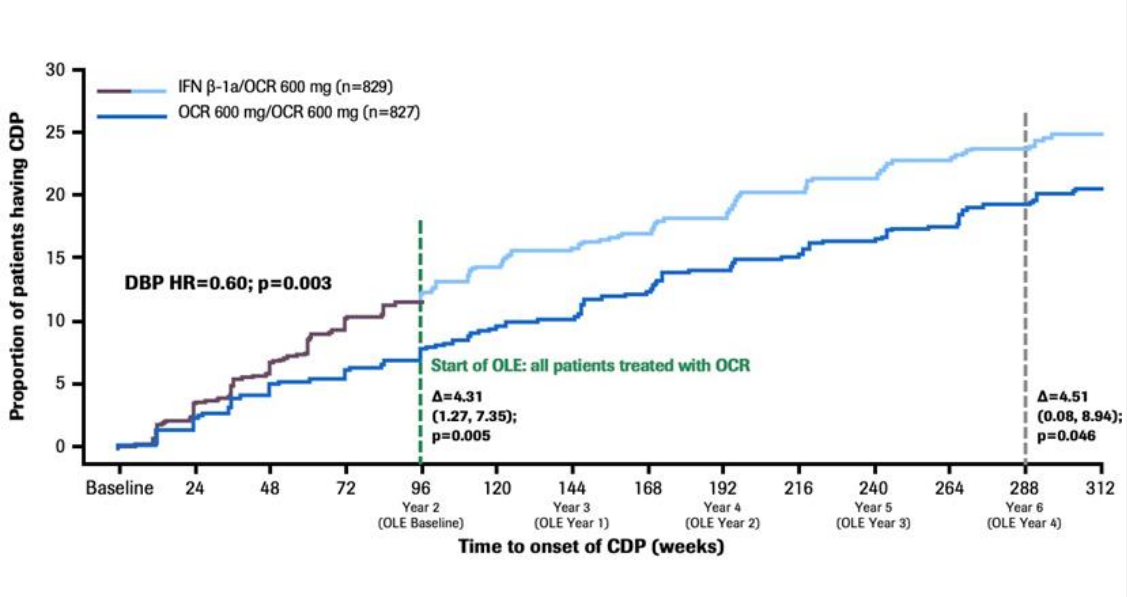


- The first and only treatment approved for both RMS and PPMS
- OCREVUS offers the first-ever approved treatment for PPMS, a highly disabling form of the disease in which disability accumulates twice as quickly as in RMS

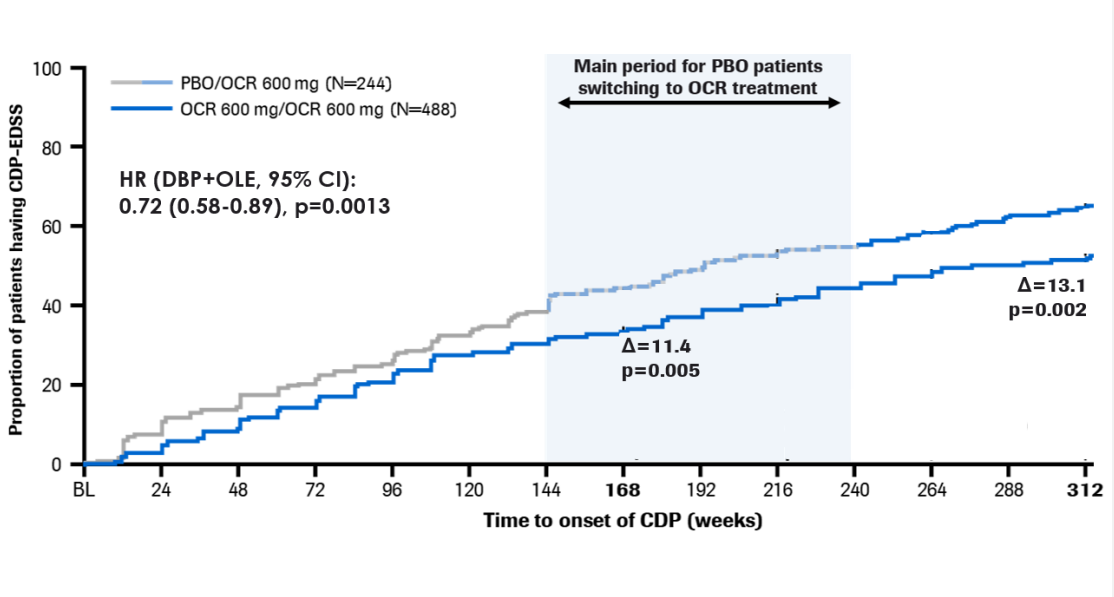
Source: [1] Roche analysis of MS prevalence epidemiological studies; RMS=relapsing multiple sclerosis; PPMS=primary progressive MS; SPMS=secondary progressive MS; CIS=clinically isolated syndrom

Long term data of >6 years show: Earlier treatment with Ocrevus significantly reduces risk of permanent disability progression

RMS: time to onset of CDP for at least 24 weeks during the DBP and OLE period of OPERA



PPMS: time to onset of CDP for at least 24 weeks during the DBP and OLE period of ORATORIO

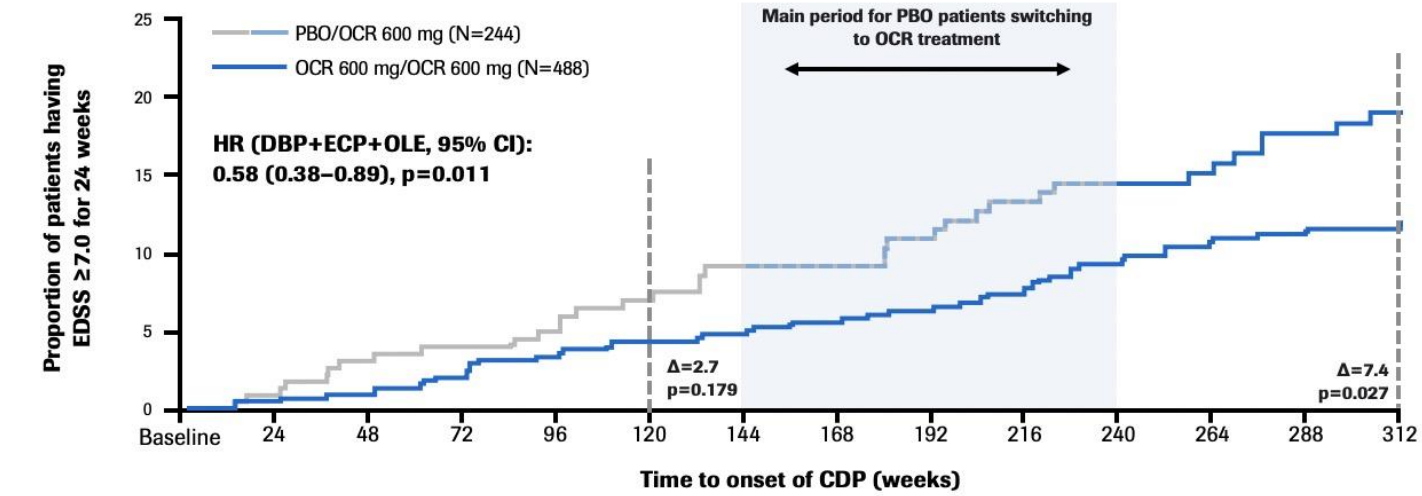


- Earlier treatment with Ocrevus significantly reduced the risk of disability progression and this effect was sustained over time

Giovannoni G. et al, ECTRIMS 2019; Wolinsky J.S. et al, ECTRIMS 2019; IFN=interferon; OCR=Ocrevus; RMS=relapsing multiple sclerosis; 24W-CDP=24 week-confirmed disability progression

Long term data of >6 years show: Earlier treatment with Ocrevus significantly reduces risk of patients needing a wheelchair (EDSS ≥7.0)

RMS: time to onset of CDP for at least 48 weeks during the DBP and OLE periods



No. of patients at risk

	Baseline	24	48	72	96	120	144	168	192	216	240	264	288	312
PBO/OCR	244	238	232	225	217	211	204	199	192	185	176	170	163	159	156	155	151	147	144	140	140	139	136	133	127	123	112
OCR/OCR	487	471	465	459	454	441	434	425	417	410	402	397	388	382	377	365	357	346	341	334	327	322	314	305	296	289	272

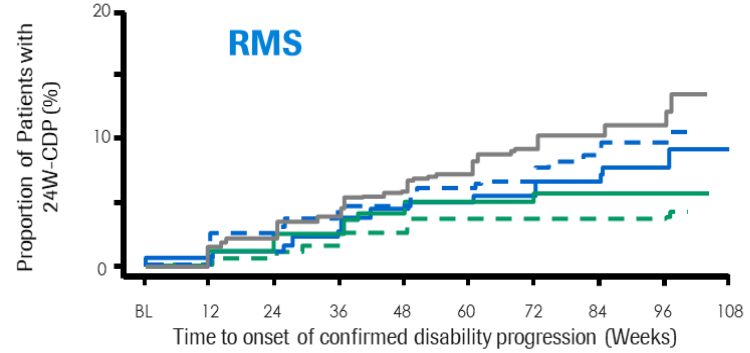
- Earlier initiation of Ocrevus therapy significantly reduced the risk of becoming wheelchair confined by 42% vs those who switched from placebo

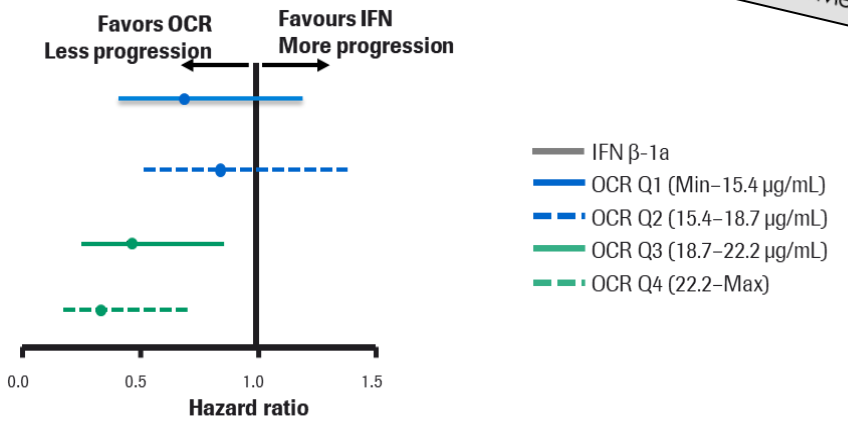
Wolinsky J.S. et al, ECTRIMS 2019; CDP=confirmed disability progression; DBP=double-blind period; ECP=extended controlled period; EDSS=Expanded Disability Status Scale; FU=follow-up; HR=hazard ratio; ITT=intention-to-treat; OCR=ocrelizumab; OLE=open-label extension; PBO=placebo

Higher Ocrevus exposure reduces risk of disability progression

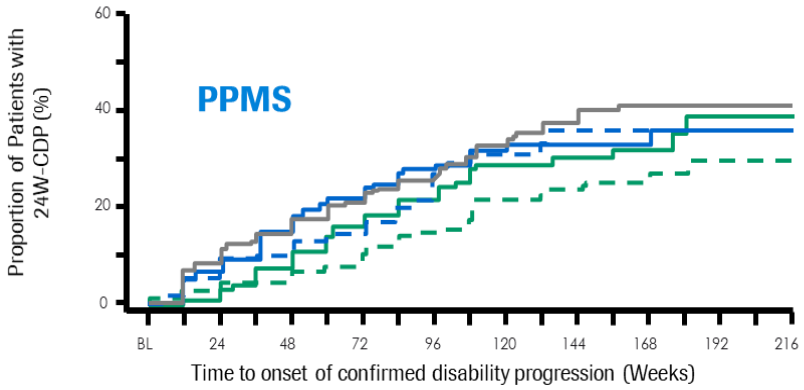
Importance of starting and maintaining approved dosing

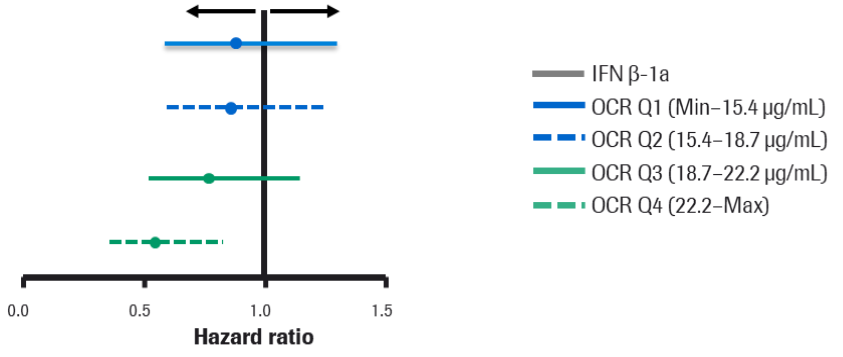
RMS (OPERA)





PPMS (ORATORIO)

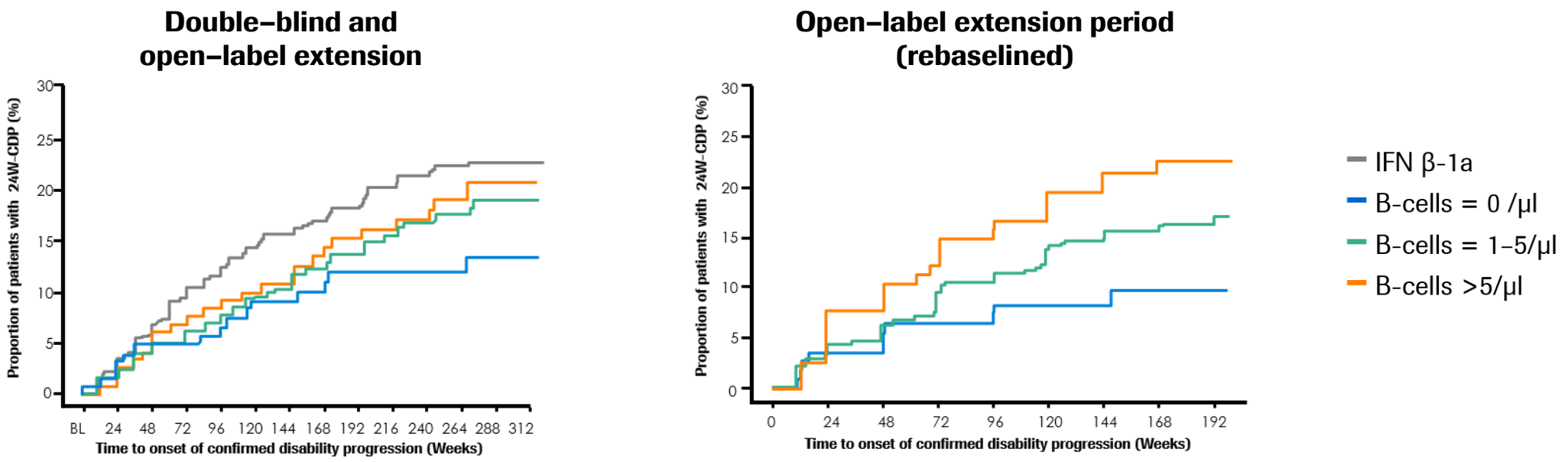




Hauser S.L. et al, AAN 2019; IFN=interferon; OCR=Ocrevus; RMS=relapsing multiple sclerosis; PPMS=primary progressive MS; Q=quartile

Importance of B-Cell depletion on disability progression

RMS (OPERA): B cell–stratified 24–week confirmed disability progression (CDP)



- Lower rates of disability progression associated with higher Ocrevus exposure and lower median B cell levels prior to the next infusion

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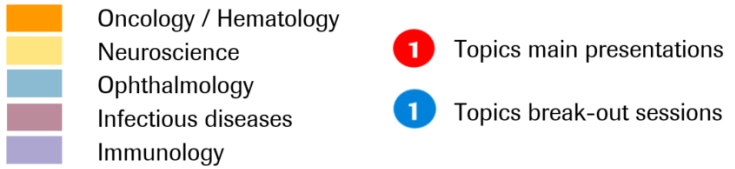

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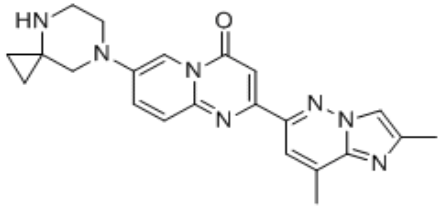
Risdiplam in type 1/2/3 spinal muscular atrophy (SMA)

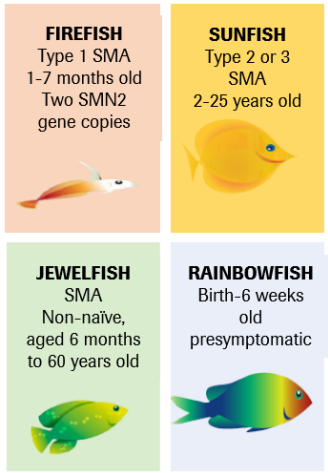
Broadest Ph III program with potentially best in class efficacy/safety profile

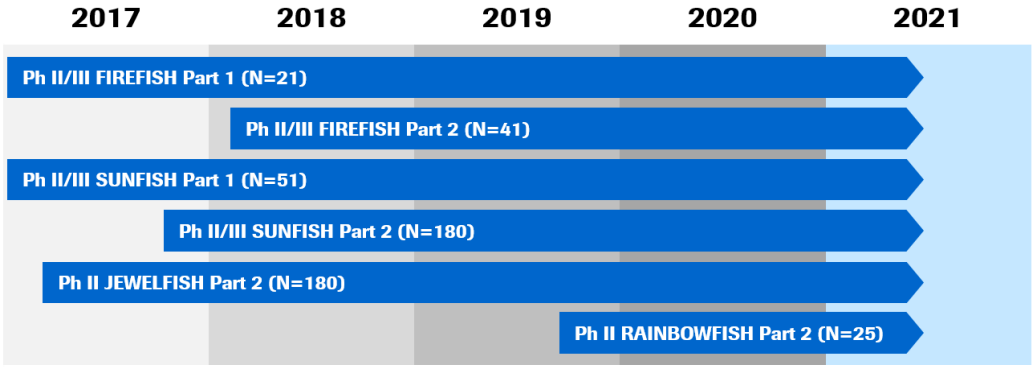
SMN2 splicing modifier



- Oral and systemically available SMN2 splicing modifier
- Durably increases SMN throughout CNS and periphery
- Potentially best in class efficacy profile
- To date well tolerated at all doses assessed

Broadest Ph III clinical program:





- Enrolment of SUNFISH and FIREFISH Part 2 is complete, and follow-up is ongoing
- First patients recruited into presymptomatic study (RAINBOWFISH)
- 30 Spinraza-treated patients btw age 1 and 60 recruited into non-naive study (JEWELFISH)
- Filing expected in 2019

Risdiplam in collaboration with PTC Therapeutics and the SMA Foundation

Risdiplam in type 1 SMA (FIREFISH Part 1)

Typical type 1 population starting treatment at 6.7 months of age

Ph III FIREFISH

- Type 1 SMA
- 1-7 months old
- Two SMN2 gene copies

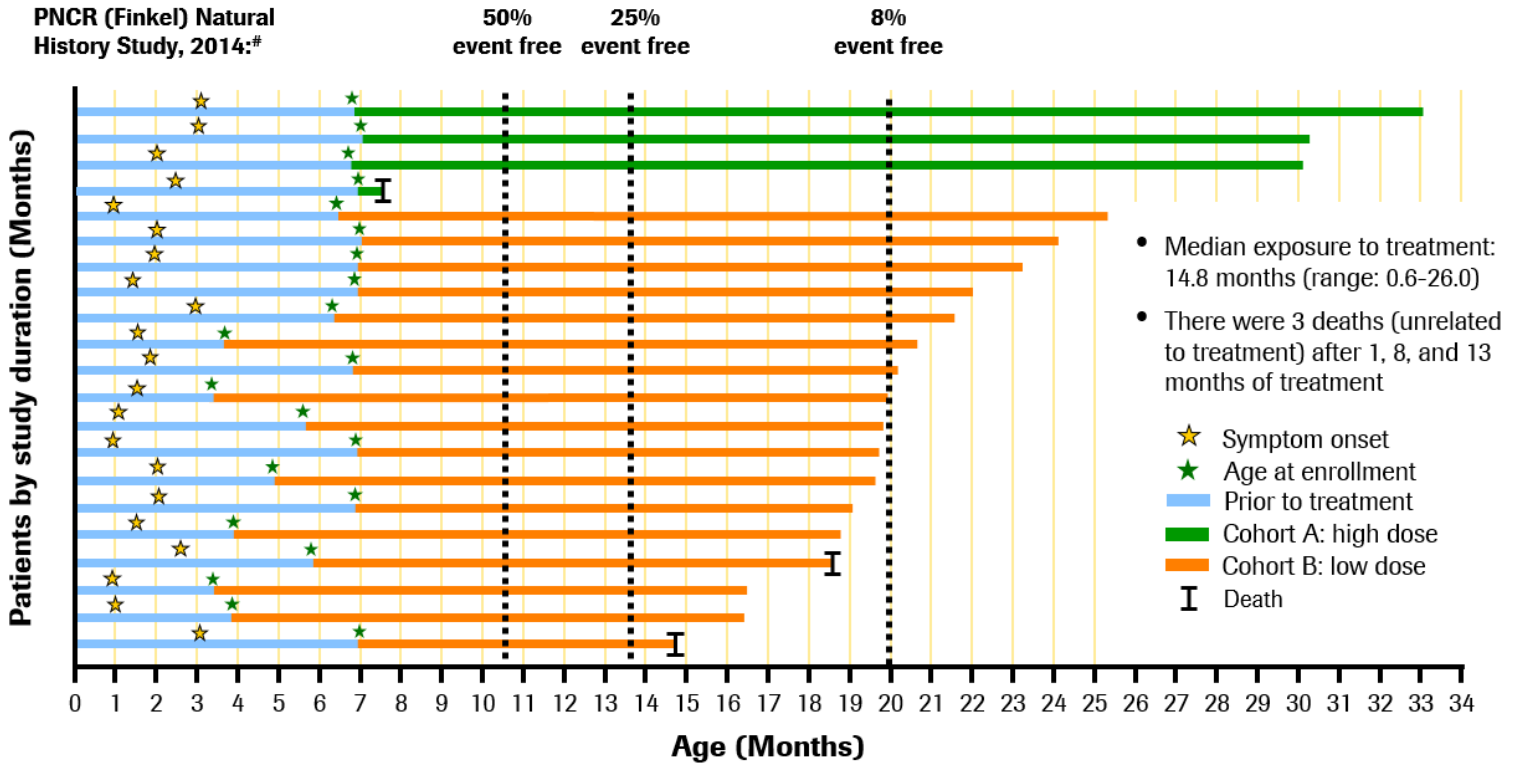
Part 1: Dose-finding period followed by open-label extension

- **Cohort A**: Low dose (n = 4)
- **Cohort B**: High dose (n = 17)
- EP: Safety, tolerability, PK and PD

Part 2: Efficacy & safety at the selected dose (n=41)

- Primary endpoint: Proportion of infants sitting without support for 5 seconds after 12 months on treatment as assessed by Gross Motor Scale of the BSID-III

19/21 infants (90.5%) were alive & event-free* after 12m treatment



Baranello et al AAN 2019; Data cut-off: 27 February 2019; # Finkel R, et al. Neurology. 2014; 83:810–817, The median age at the combined endpoint for subjects with two *SMN2* copies was 10.5 months (IQR 8.1–13.6); event free is defined as alive and no need for permanent ventilation (defined as ≥16 hours per day continuously for ≥2 weeks); * 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)

Risdiplam in type 1 SMA (FIREFISH Part 1)

Summary of 12 months of treatment

Cohort A+B (all infants)

90.5%
(19/21)
of infants are alive and event free* after 12 months of treatment

0
infants lost the ability to swallow†

0
infants reached permanent ventilation/required tracheostomy

No drug-related safety findings leading to withdrawal to date

Cohort B (high dose)

41%
(7/17)
were able to sit without support for at least 5 seconds (as assessed by BSID-III)

1/17
infants
were able to stand supporting their weight (as assessed by HINE-2)

59%
(10/17 infants)
had a CHOP-INTEND score ≥40

*Event free 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). †1 infant was unable to swallow at baseline. 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; SMA, spinal muscular atrophy.

Risdiplam in type 2/3 SMA (SUNFISH Part 1)

Dose-finding in broad population starting at median of 7 years

Ph III SUNFISH

- Type 2 or 3 SMA
- 2-25 years old

Part 1: Dose-finding period followed by open-label extension

- Primary endpoints: Safety, tolerability, PK and PD
- Exploratory: efficacy

Part 2: Efficacy & safety at the selected dose (n=180)

- Placebo-controlled (2:1) for 12 months
- Primary endpoint: MFM

12 months after treatment start exploratory efficacy greatly exceeds natural history in younger and older patients

Domain 1: standing, transfers and ambulation

Domain 2: axial and proximal motor function

Domain 3: distal motor function

12 months change from baseline	SUNFISH Part 1			Natural history SMA
Age range (years)	2–11 (n=24)†	12–25 (n=19)‡	2–25 (n=43)*	2–30 (n=39)
MFM32 change from baseline, mean (SD)	3.47 (3.77)	1.64 (3.43)	2.66 (3.70)	-1.44 (3.68)
≥3 point change at month 12, n (95% CI)	17 **(71%)** (49–87%)	8 **(42%)** (20–67%)	25 **(58%)** (42%–73%)	3 **(7.6%)** (2%–21%)

- The MFM32 is a 32 item assessment classified into 3 domains; Each item is measured on a 4-point scale with a total score of 0–100 and with higher scores indicating greater motor function.
- The MFM32 is validated measuring motor function in patients with neuromuscular diseases incl. SMA[1,2]

Mercuri et al, AAN 2019;* Excludes seven patients who performed the MFM20 assessment at baseline and one patient who had dropped out of the study prior to the Month 12 visit; † excludes seven patients who performed the MFM20 assessment at baseline; ‡ excludes one patient who had dropped out of the study prior to the Month 12 visit. Based on change from adjusted baseline. SUNFISH data cut-off: 9th Jan 2019; MFM=Motor Function Measure. 1. Bérard C, et al. Neuromuscul Disord. 2005; 15:463–470; 2. Vuillerot C, et al. Ann Phys Rehabil Med. 2013; 56:673–686

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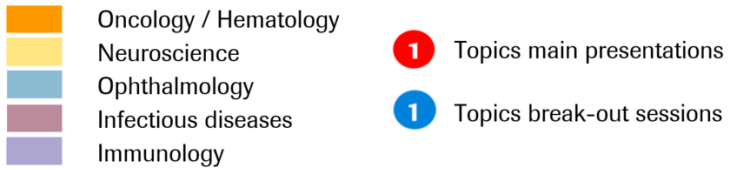

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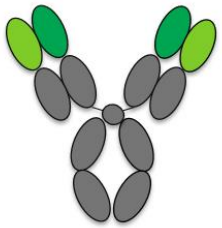
Satralizumab in NMOSD

Recycling Ab for maximal inhibition of IL-6 signaling

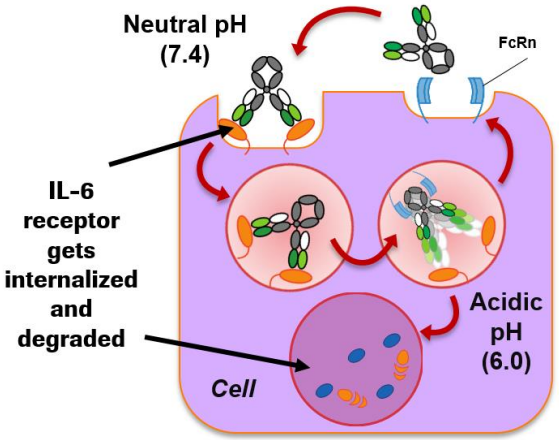
FDA BTD

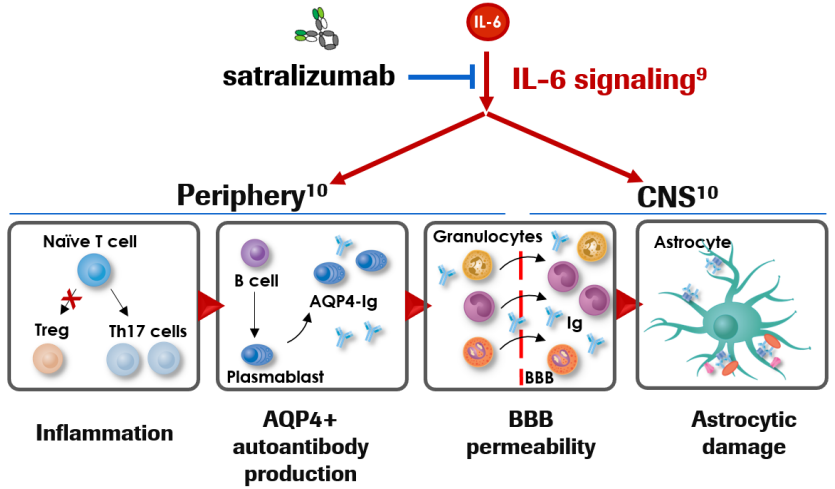
Anti-IL-6 receptor mAb



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

Recycling Ab for blocking IL-6 signaling in NMOSD:





- NMOSD is a debilitating, chronic, autoimmune CNS disease with lesions in the optic nerves and spinal cord
- IL-6 is thought to impact B-cell mediated pathogenesis incl. AQP4 auto-antibody production
- Robust, durable efficacy demonstrated in AQP4+/- patients either as add-on therapy to SOC (Ph III SAkuraSky) or as monotherapy (Ph III SAkuraStar)

NMOSD=neuromyelitis optica spectrum disorder; CNS=central nervous system; AQP4=aquaporin; SOC=standard of care

Neuromyelitis optica spectrum disorder (NMOSD)
A rare and debilitating autoimmune CNS disease

IL-6 is a key driver in the pathogenesis of NMOSD

~5 **Per 100,000**

1/2 **Blind within 5 years**
Require wheelchair

9/1 **Female/male**

Clinical manifestation

- Optic neuritis and/or longitudinally extensive transverse myelitis
- Blindness, severe motor disability, sensory disturbances, neuropathic pain
- Relapsing: Disability can accumulate with each subsequent attack
- Anti-AQP4 autoantibodies in 70 to 80% of patients
- ~40% of patients with NMOSD are first misdiagnosed as having MS

Satralizumab efficacy/safety profile

✓ **Highly effective**
- Comparable efficacy to best in disease treatments

✓ **Flexible and convenient**
- Only treatment studied as monotherapy and in combination with immunosuppressants
- Convenient Q4w SC dosing
- Broadest flexibility on patient profile (AQP4+/-, only treatment for adolescent)
- Unique mechanism of action

✓ **Favourable safety profile**
- Lower rate of infections incl. serious infections

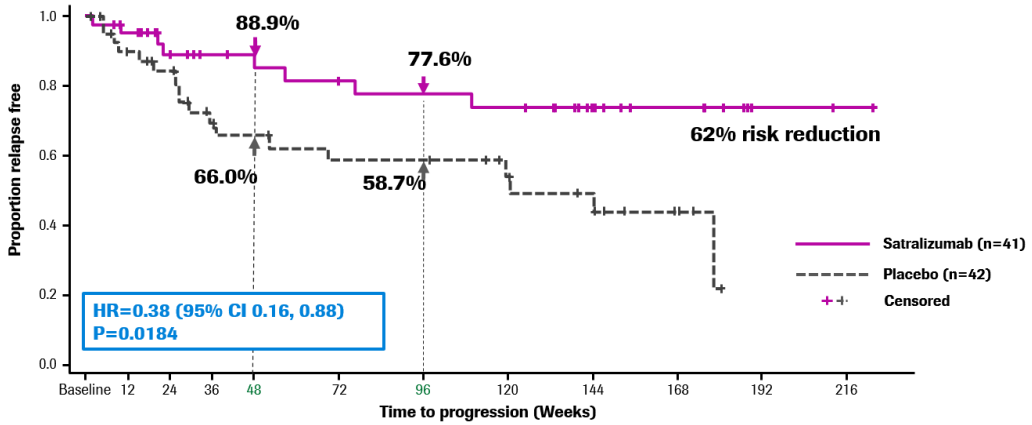
AQP4=aquaporin 4; MOA=mechanism of action; Q4W=every 4 weeks; SC=subcutaneous

Satralizumab as add-on therapy in NMOSD

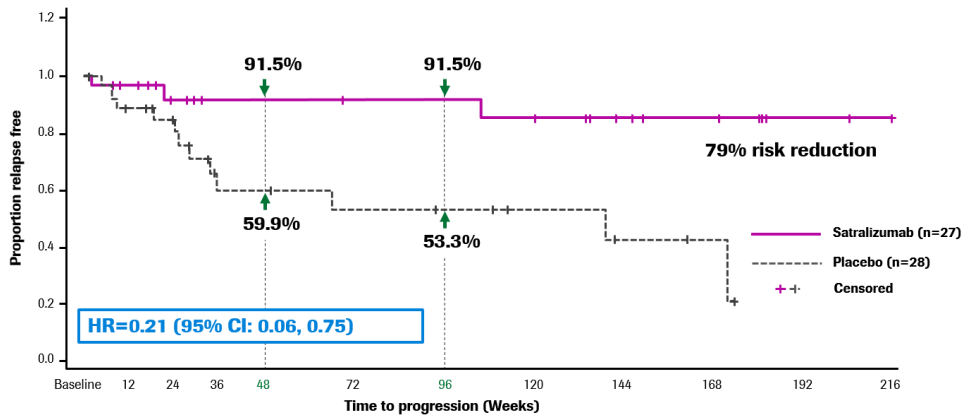
79% relapse risk reduction in AQP4+ patients

Ph III results add-on therapy (SAkuraSky):

Risk of protocol-defined relapse (ITT population)



Risk of protocol-defined relapse (AQP4+ patients)



- As add-on therapy to baseline immunosuppressive therapy risk of relapse in the ITT population was reduced by 62%, in the AQP4+ patients by 79% with 91.5% of AQP4+ patients being relapse free at 48 and 96 weeks
- Efficacy was generally consistent across pre-specified subgroups

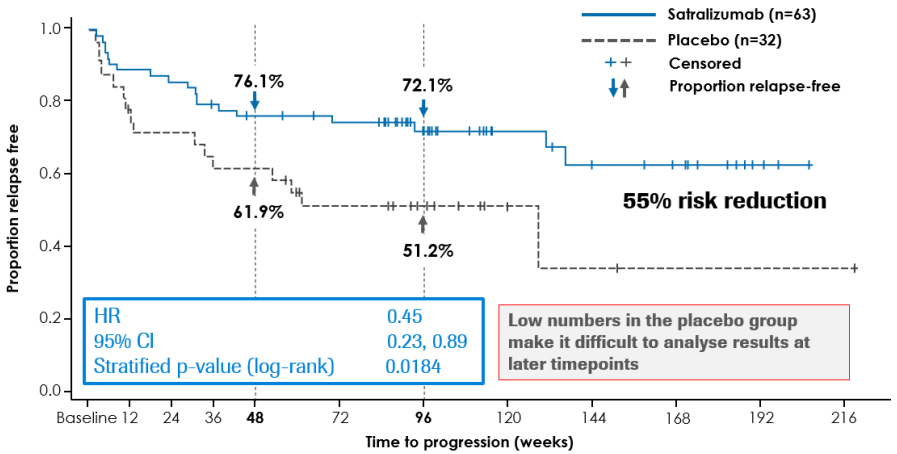
Yamamura et al. ECTRIMS 2018; Analysis based on ITT population; p-value based on log-rank test stratified by geographic region and baseline relapse rate. Protocol-defined relapse as adjudicated by the independent clinical endpoint committee. EDSS/FSS was assessed within 7 days of relapse reporting. CI=confidence interval; EDSS=Expanded Disability Status Scale; FSS=functional system scores; ITT=intent to treat

Satralizumab as monotherapy in NMOSD

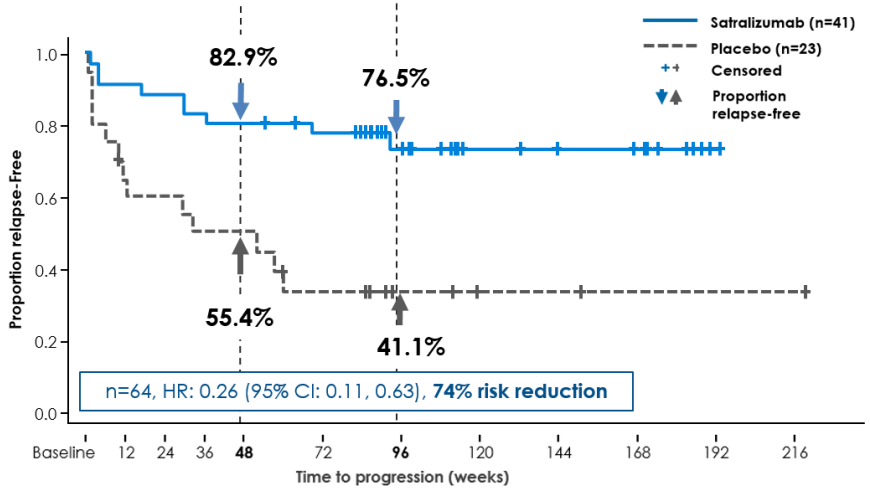
74% relapse risk reduction in AQP4+ patients

Ph III results monotherapy (SAkuraStar):

Risk of protocol-defined relapse (ITT population)



Risk of protocol-defined relapse (AQP4+ patients)



- Relapse risk was reduced by 55% in the ITT population with 76% and 72% of patients being relapse-free at week 48 and 96, respectively
- Relapse risk was reduced by 74% in AQP4+ patients (not affected by prior therapy or most recent attack type) with 83% and 77% being relapse-free at week 48 and 96, respectively

Bennett J.L. et al., ECTRIMS 2019; Analysis based on ITT population; p-value (based on log-rank test) and hazard ratio (using Cox proportional-hazards model) stratified by prior therapy for prevention of NMOSD attack (B-cell-depleting or immunosuppressants/other) and by most recent attack in the year prior to screening (first attack vs relapse); CI=confidence interval; HR=hazard ratio; ITT=intention to treat

Late stage pipeline update

Topics covered in presentations and break-out sessions

1. **Hematology franchise**
   - CLL: Venclexta Gazyva
   - DLBCL: Polivy, Venclexta
   - NHL, DLBCL: mosunetuzumab, CD20xCD3
   - AML: Venclexta, idasanutlin
   - MM: Venclexta

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   - ALK+: Alecensa
   - ROS1+/NTRK+: Rozlytrek

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   - Hemlibra

7. **Neuroscience**
   - MS: Ocrevus update
   - SMA: risdiplam
   - NMOSD: satralizumab
   - Huntington's disease: HTT-ASO
   - Autism: balovaptan
   - Parkinson's disease: prasinezumab

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   - Ulcerative colitis: etrolizumab
   - Crohn's disease: etrolizumab
   - Food allergy: Xolair
   - Nasal polyps: Xolair

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   - Influenza A/B: baloxavir marboxil

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   - DME, nAMD: faricimab
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   - Choroideremia: Gene therapy

Oncology / Hematology
Neuroscience
Ophthalmology
Infectious diseases
Immunology

1 Topics main presentations
1 Topics break-out sessions

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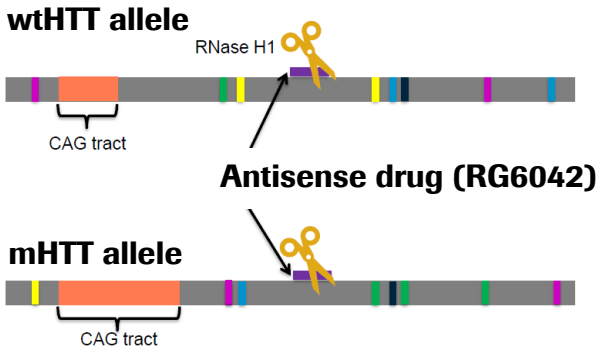
HTT-ASO in Huntington's disease

First drug to reduce toxic mHTT

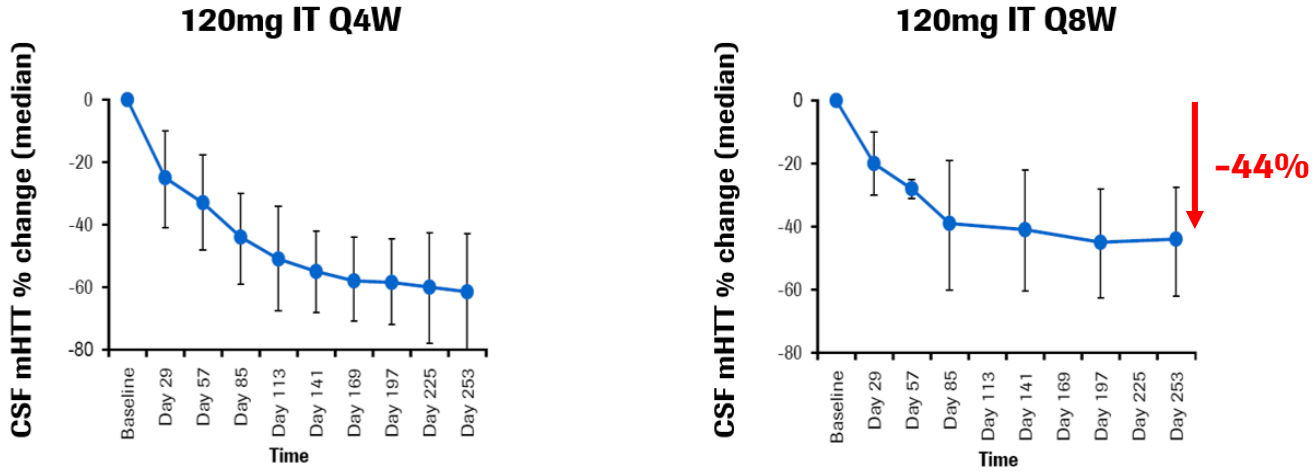
Antisense RNA targeting total HTT



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

Phase II update:

mHTT CSF levels from 9 month OLE cut



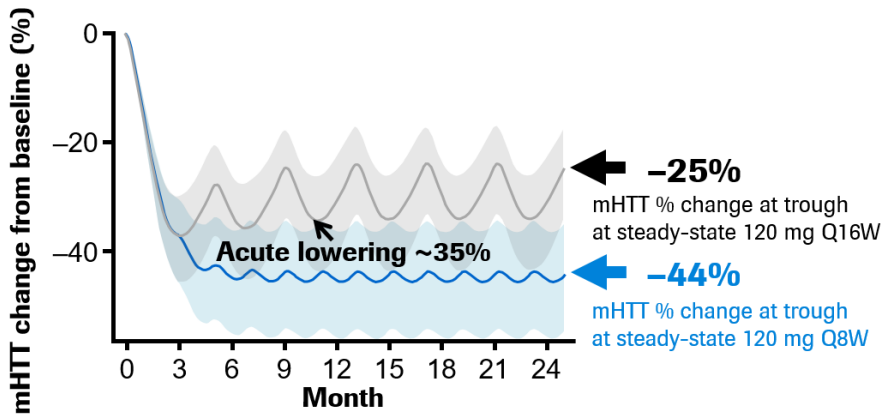
- 9 month OLE data show sustained lowering of CSF mHTT in both dosing regimens (Q4W; Q8W) achieving the target reduction range of 30-50%
- Safe and well tolerated with no dose-limiting toxicities identified

Sanwald Ducray P. et al, AAN 2019; 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

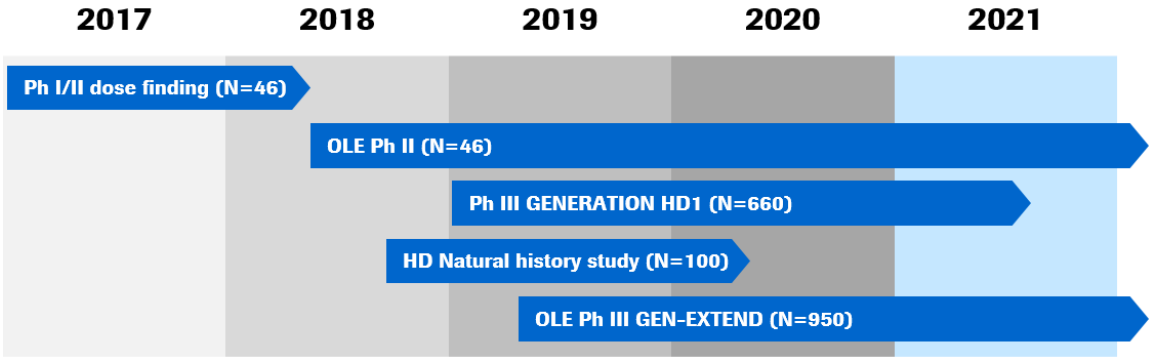
HTT-ASO in Huntington's disease

Ph III development program underway

Simulation of Q8W and Q16W dosing to achieve pharmacologically relevant effect (120 mg IT)



Ph III development program



- Ph II OLE data and PK/PD modelling led to amendment of Ph III (GENERATION HD1) study to allow less frequent dosing (Q8W; Q16W)
- First patients recruited for new Ph III protocol in Q3
- Ph II OLE and HD Natural history study continue to provide data to inform the development program

Sanwald Ducray P. et al, AAN 2019; mHTT=mutant huntingtin; NHP=nonhuman primate; OLE=open-label extension; PD=pharmacodynamic; PK=pharmacokinetic; Q8W=every two months; Q16W=every four months; HTT-ASO licensed from IONIS Pharmaceuticals

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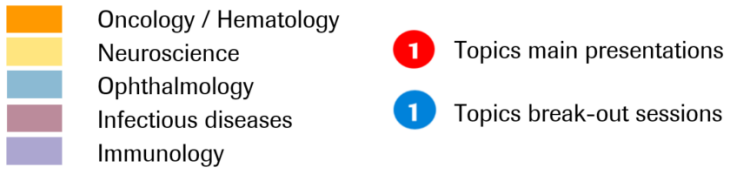

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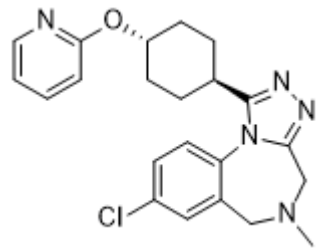
Balovaptan in autism spectrum disorder (ASD)

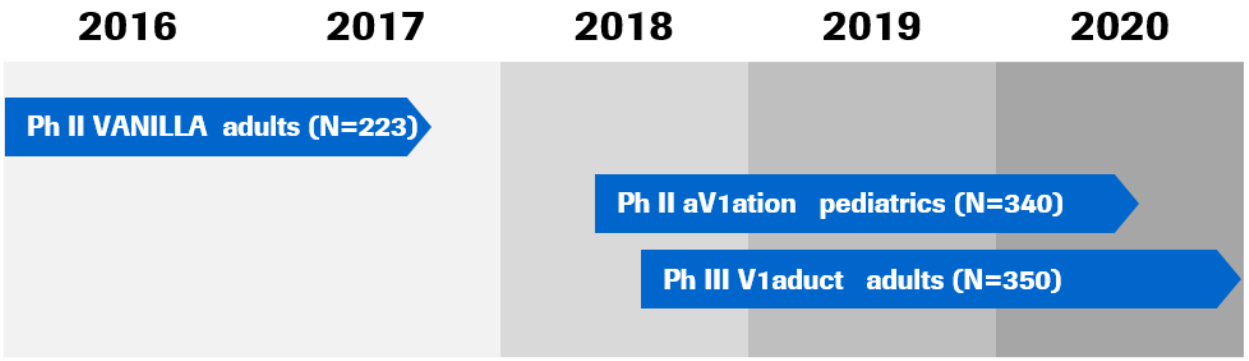
Early positive data from first Ph II study in adults

V1a receptor antagonist



- Oral, selective V1a receptor antagonist
- Vasopressin V1a receptor modulates social behavior and is implicated in ASD
- Good pharmacokinetic profile and well tolerated in Ph I and II studies

Phase III development program:



- Ph II (VANILLA) in adult men: Primary endpoint (SRS-2) not met; however dose dependent treatment effect on the Vineland™-II composite score shows significant improvement in socialization and communication; Published in *Science Translational Medicine*
- Digital biomarkers development for autism to quantify change in core ASD symptoms
- Ph II study (aV1ation) in children and adolescents with ASD ongoing, with Vineland™-II being the primary endpoints; Results expected in 2020
- Ph III trial (V1aduct) in adults with ASD on-going; results expected in 2020

ASD=autism spectrum disorder; SRS-2=social responsiveness scale-2; Vineland™-II=Vineland Adaptive Behavior Scale 2nd Edition

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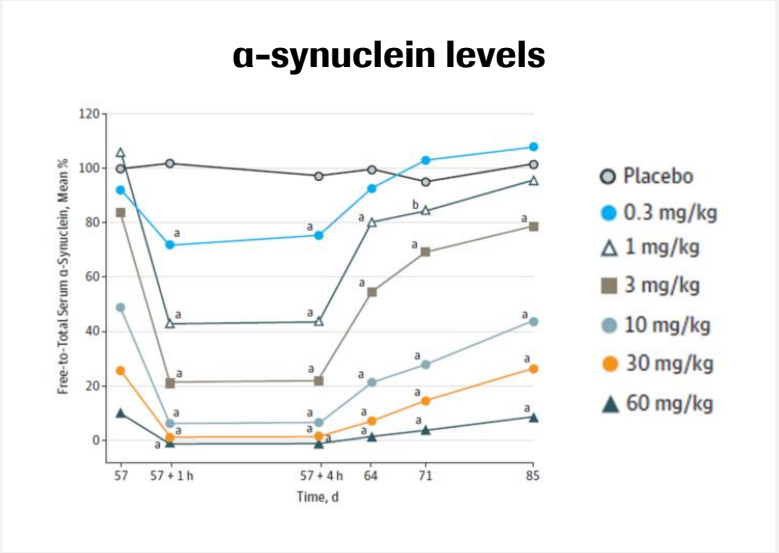
Prasinezumab in Parkinson's disease

First drug to reduce toxic forms of α-synuclein

Anti-α-synuclein mAb

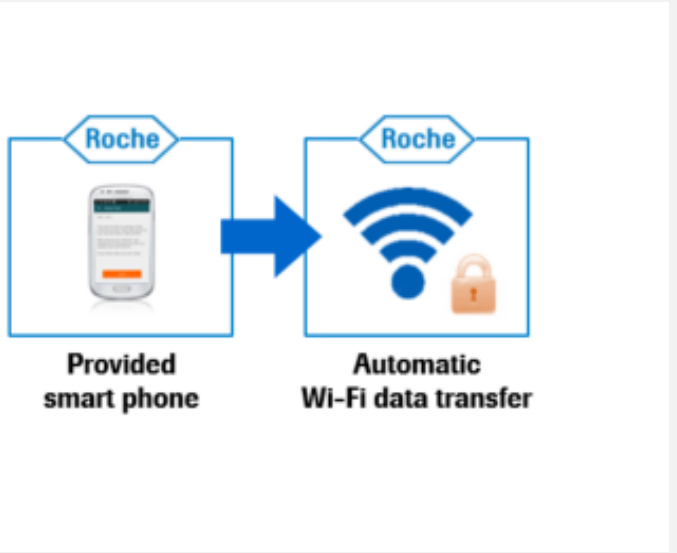
- Humanized mAb designed to target aggregated forms of α-synuclein
- Potentially inhibiting neuron-to-neuron transfer of presumed pathogenic forms of α-synuclein, resulting in neuronal protection and slowing progression

Ph I results:



- 97% reduction of free α-synuclein serum level after single infusion at highest dose
- Prasinezumab reaches CSF concentrations expected to engage extracellular aggregated α-synuclein in the brain
- Digital endpoints in development for remote and frequent monitoring of symptoms
- Ph II data from Part 1 of the study expected in 2020

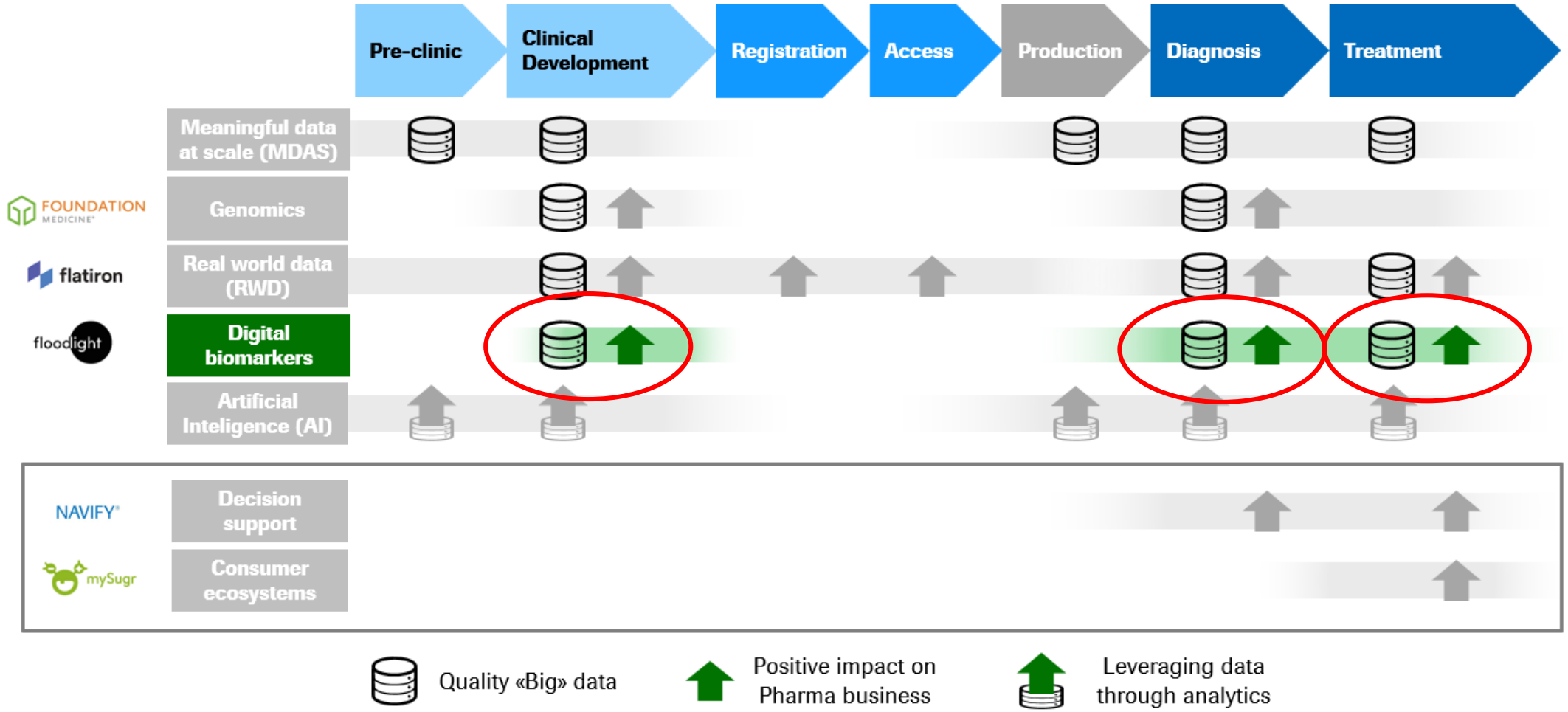
Digital endpoint development:



Jankovic J. et al, JAMA Neurol. 2018 Jun 18; Lipsmeier et al, Mov.Dis. April 2018; CSF=cerebrospinal fluid; Prasinezumab partnered with Prothena

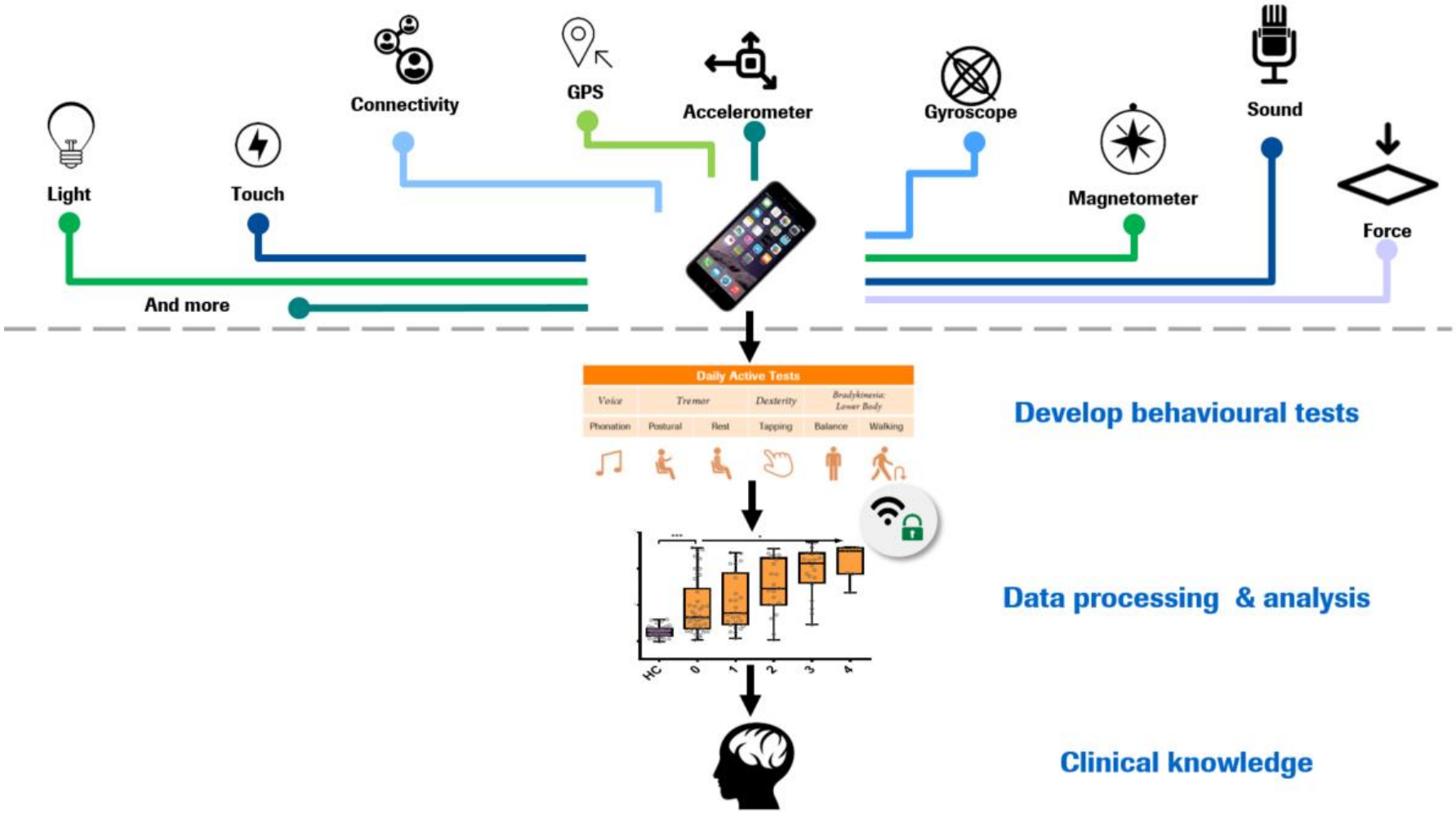
Developing digital biomarkers in Neuroscience

Digital endpoints for drug development, improved diagnosis & treatment



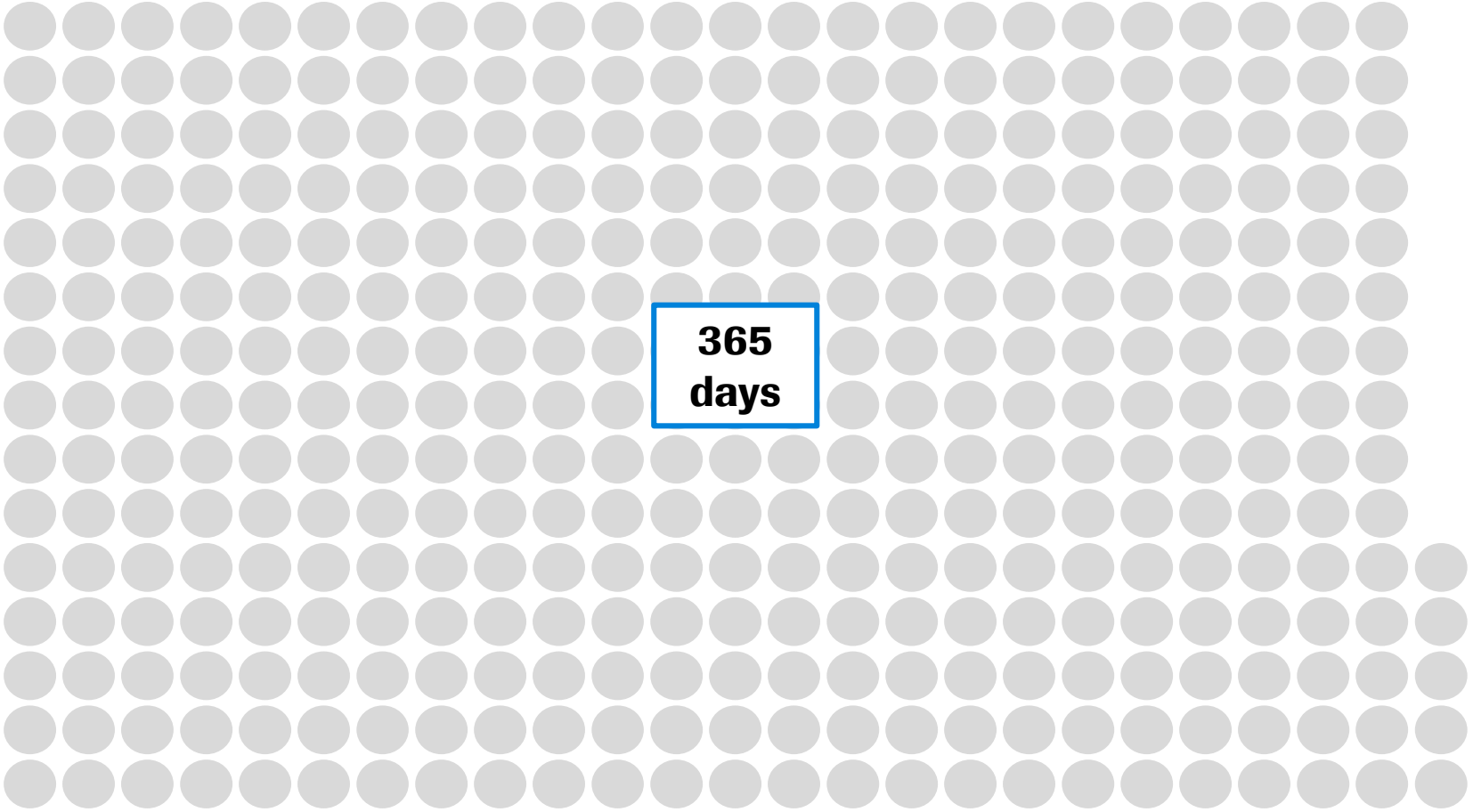
Developing digital biomarkers in Neuroscience

Collect, process, analyse data to gain clinical knowledge



Digital biomarkers allow remote patient monitoring

Longitudinal resolution of symptom dynamics & real-world performance



Day in the life of a patient with weak symptoms

Digital biomarkers allow remote patient monitoring

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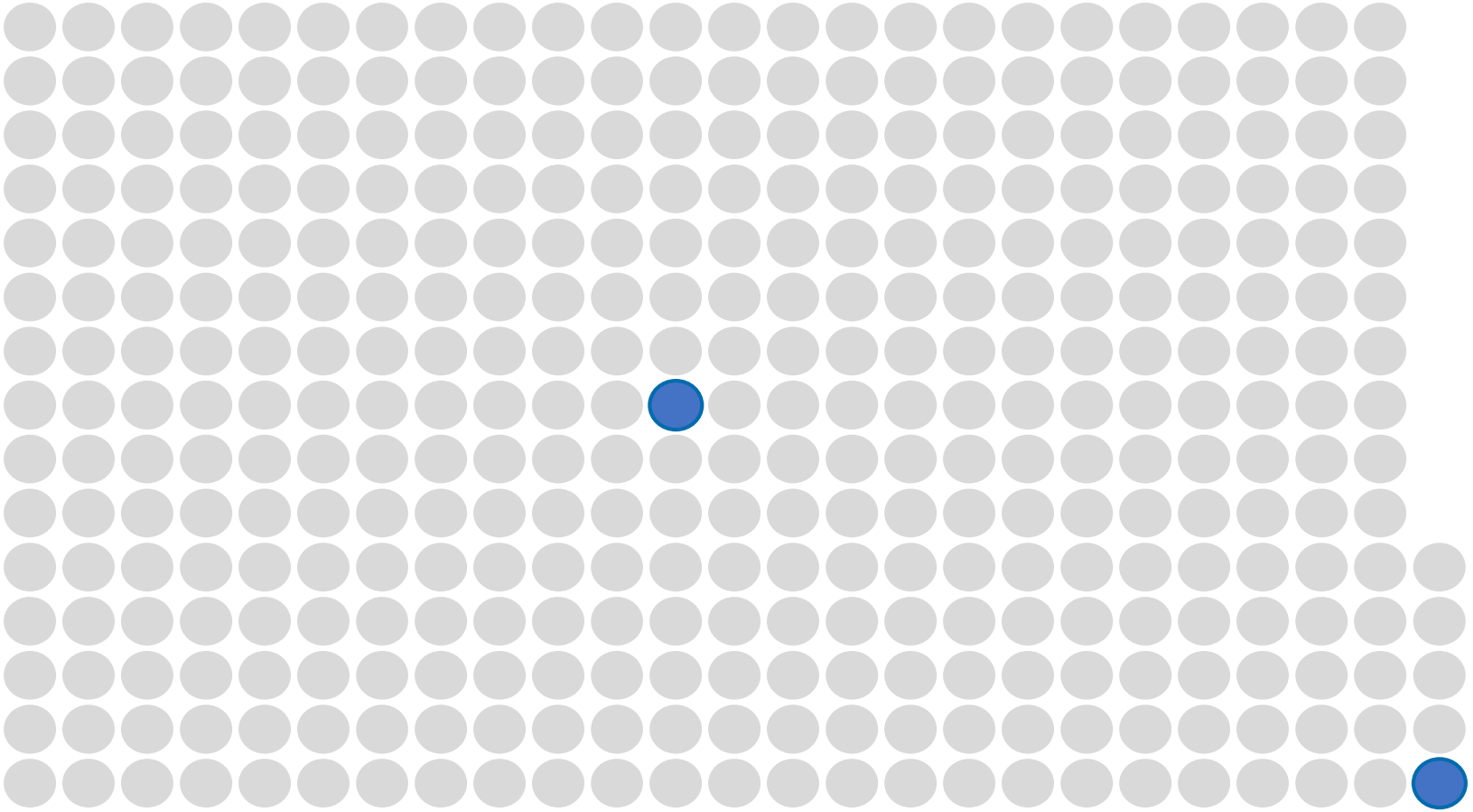

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Day with a visit to the clinic or physician

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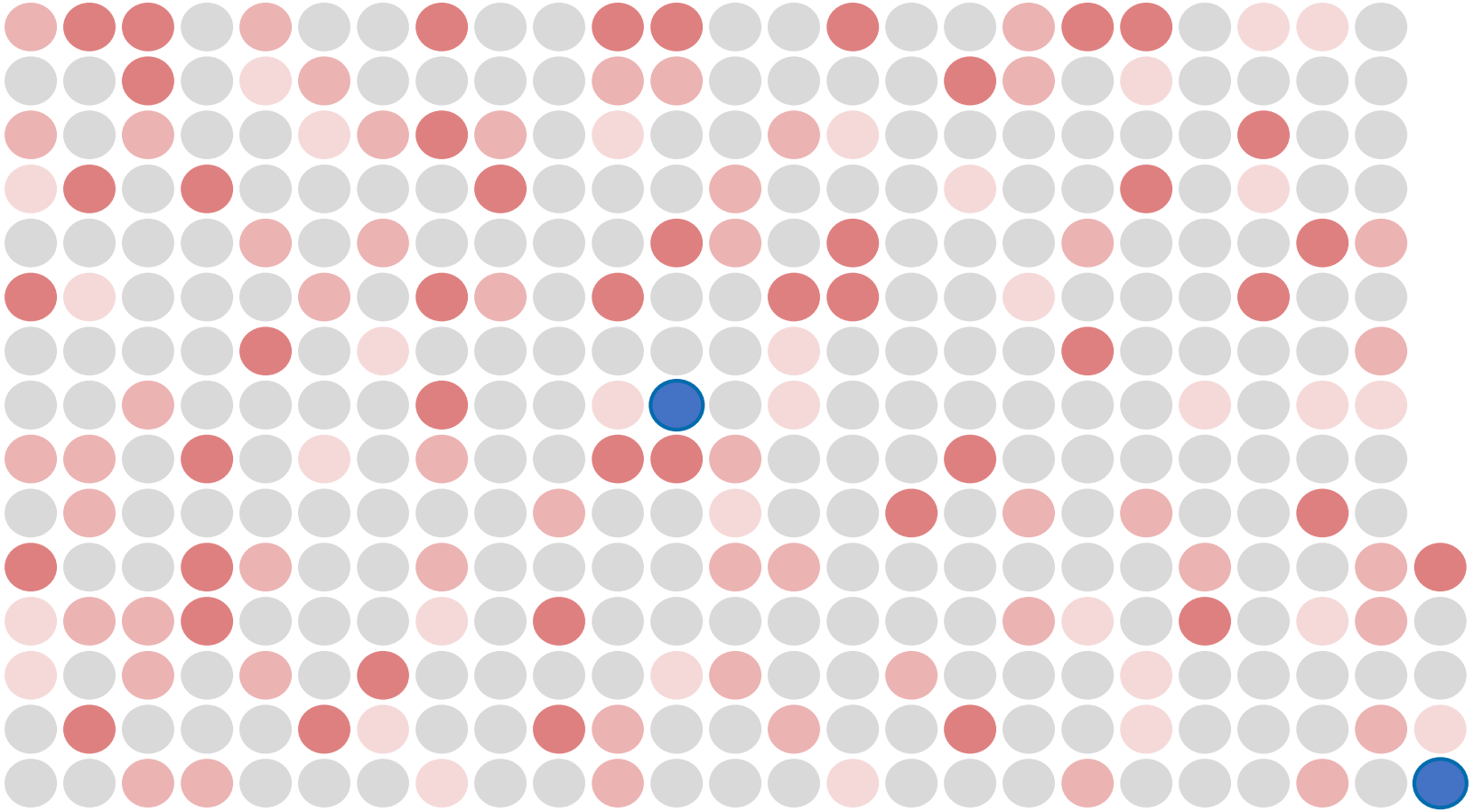

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Day with stronger symptoms

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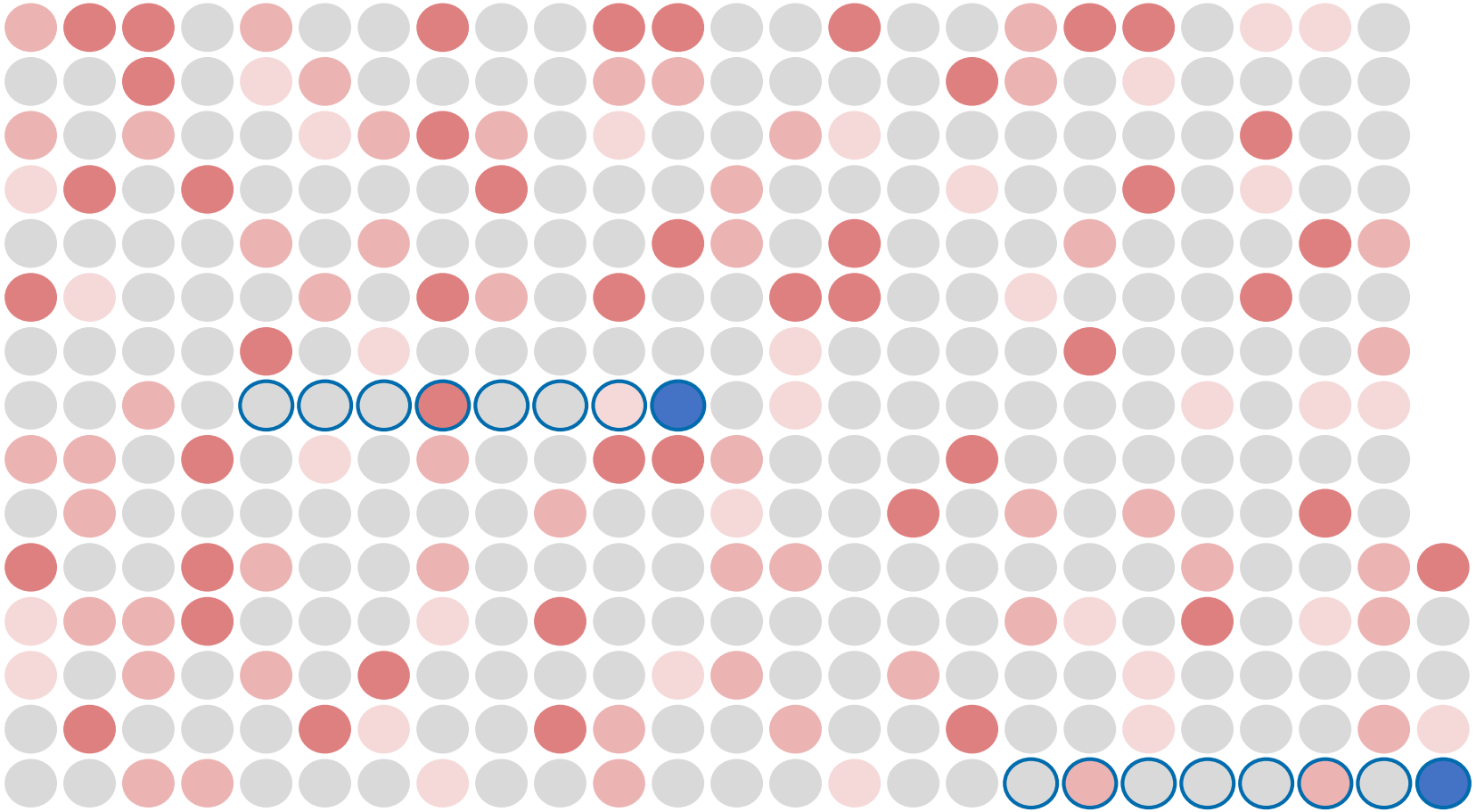


Day in the life of a patient with weak symptoms

Day with a visit to the clinic or physician

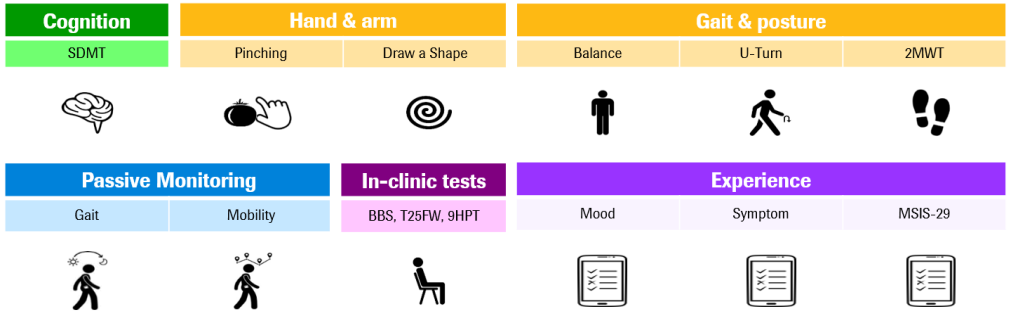
Day with stronger symptoms

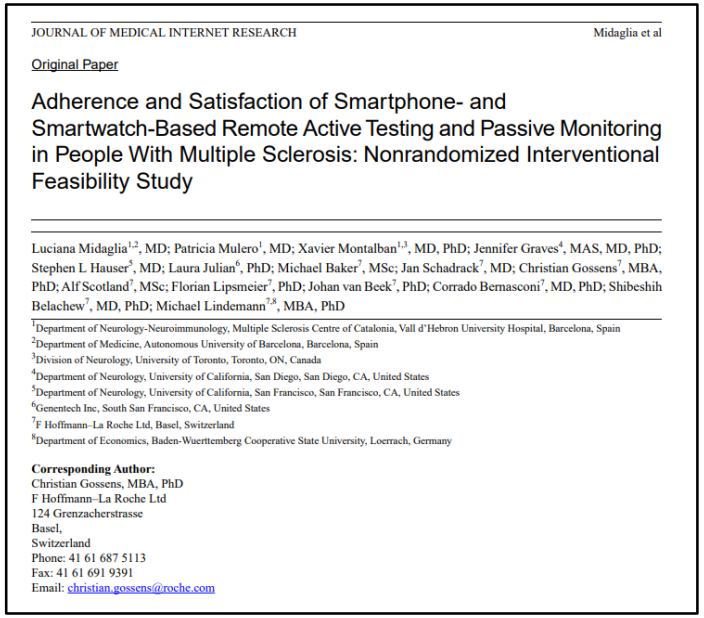
Patients' recall period

Digital biomarkers in Multiple sclerosis

Floodlight: A neurologist in your pocket

Defining new endpoints and improving standard of care





JOURNAL OF MEDICAL INTERNET RESEARCH — Midaglia et al

Original Paper

Adherence and Satisfaction of Smartphone- and Smartwatch-Based Remote Active Testing and Passive Monitoring in People With Multiple Sclerosis: Nonrandomized Interventional Feasibility Study

Luciana Midaglia[1,2], MD; Patricia Mulero[1], MD; Xavier Montalban[1,3], MD, PhD; Jennifer Graves[4], MAS, MD, PhD; Stephen L Hauser[5], MD; Laura Julian[6], PhD; Michael Baker[7], MSc; Jan Schadrack[7], MD; Christian Gossens[7], MBA, PhD; Alf Scotland[7], MSc; Florian Lipsmeier[7], PhD; Johan van Beek[7], PhD; Corrado Bernasconi[7], MD, PhD; Shibeshih Belachew[7], MD, PhD; Michael Lindemann[7,8], MBA, PhD

[1]Department of Neurology-Neuroimmunology, Multiple Sclerosis Centre of Catalonia, Vall d'Hebron University Hospital, Barcelona, Spain
[2]Department of Medicine, Autonomous University of Barcelona, Barcelona, Spain
[3]Division of Neurology, University of Toronto, Toronto, ON, Canada
[4]Department of Neurology, University of California, San Diego, San Diego, CA, United States
[5]Department of Neurology, University of California, San Francisco, San Francisco, CA, United States
[6]Genentech Inc, South San Francisco, CA, United States
[7]F Hoffmann-La Roche Ltd, Basel, Switzerland
[8]Department of Economics, Baden-Wuerttemberg Cooperative State University, Loerrach, Germany

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Christian Gossens, MBA, PhD
F Hoffmann–La Roche Ltd
124 Grenzacherstrasse
Basel,
Switzerland
Phone: 41 61 687 5113
Fax: 41 61 691 9391
Email: christian.gossens@roche.com

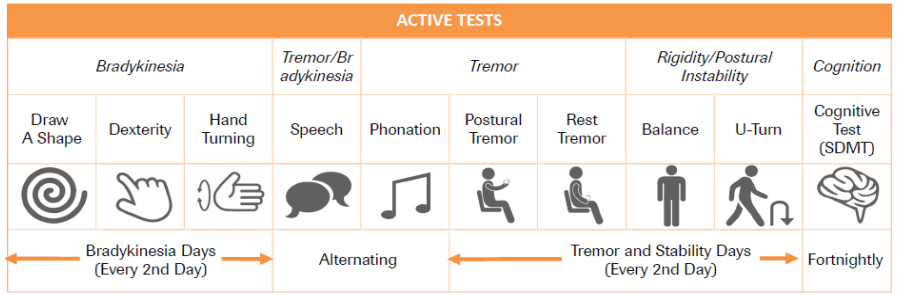
Validating digital outcomes with traditional clinical endpoints for measuring disease progression

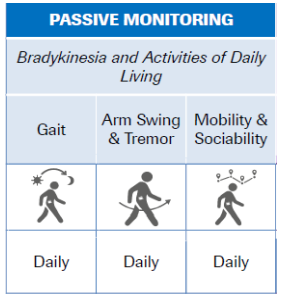
- Ph IIIb (ORATORIO-HAND), placebo-controlled: Ocrevus in PPMS including patients in wheelchairs and using upper limb function as 1EP
- Ph IIIb (CONSONANCE and ENSEMBLE) studies with Ocrevus across progressive MS spectrum
- FLOODLIGHT OPEN: Large (N=~10.000) non-interventional global study detecting and measuring progression initiated in Q2 2018

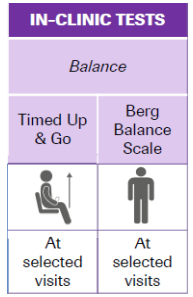
Midaglia L. et al., J Med Internet Res. 2019 Aug 30;21(8):e14863. doi: 10.2196/14863; MS=multiple sclerosis; PPMS=primary progressive MS; 1EP=primary end point

Digital biomarkers in Parkinson's disease

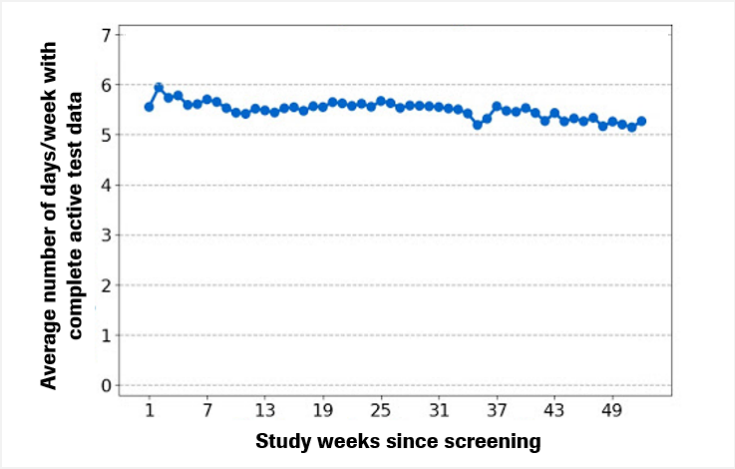
Continuous monitoring during Ph II development (PASADENA)



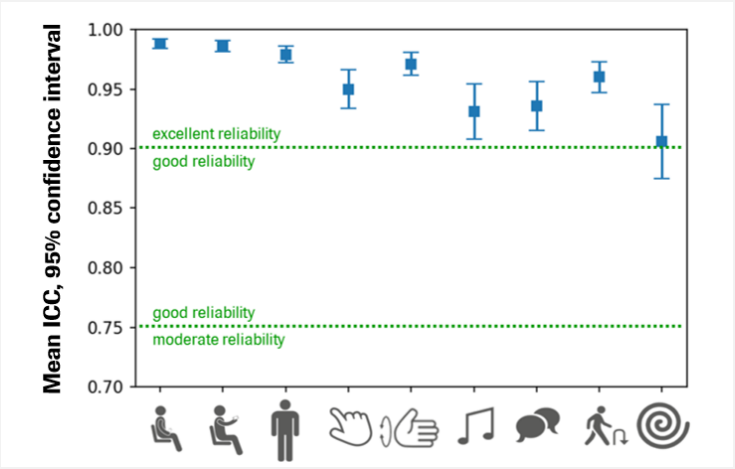




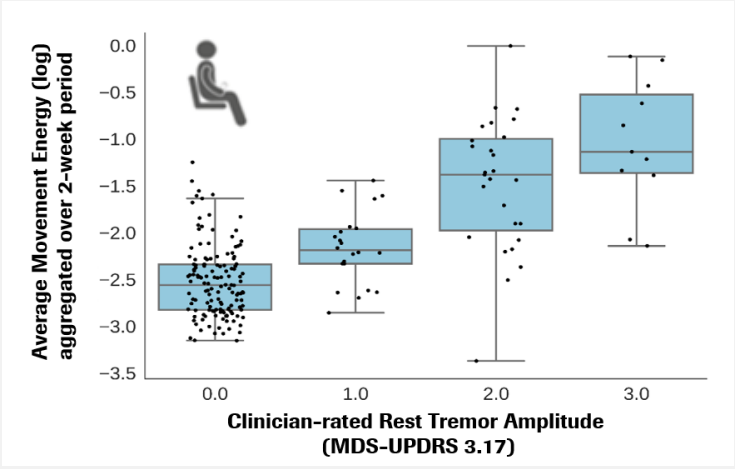
High adherence: Active tests performed on 5–6 days/week



Excellent test-retest reliability



Strong clinical relationship: All active tests significant ($p \leq 0.001$)



Taylor et al., Oral Presentation at ADPD 2019

Digital biomarker development in Neuroscience

Describing abnormalities across diseases

Broad clinical development program in Neuroscience

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

MS

SMA
Phase II/III (SUNFISH)

Huntington's disease
Phase II

Parkinson's disease
Phase I

Parkinson's disease
Phase II

Doing now what patients need next