AAN highlights 2020

Roche Analyst Audio Webcast

Basel, 28 April 2020

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1 pricing and product initiatives of competitors;
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3 delay or inability in obtaining regulatory approvals or bringing products to market;
4 fluctuations in currency exchange rates and general financial market conditions;
5 uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6 increased government pricing pressures;
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9 litigation;
10 loss of key executives or other employees; and
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Welcome
Karl Mahler, Head of Investor Relations and Group Planning

Risdiplam: FIREFISH part 2 – efficacy and safety in infants with type 1 SMA
Prof. Laurent Servais, MDUK Oxford Neuromuscular Center, Department of Paediatrics, University of Oxford, UK

Risdiplam: Update on clinical development program in patients with Type 1, 2 & 3 SMA

OCREVUS: Long-term disability progression and thalamic atrophy data in MS
Shorter infusion (ENSEMBLE PLUS) data and regulatory update
Paulo Fontoura, M.D. Ph.D., Global Head Neuroscience and Rare Diseases Clinical Development

Q&A
Karl Mahler, Head of Investor Relations and Group Planning

Welcome

Karl Mahler

Head of Investor Relations and Group Planning

Rich newsflow ahead – expect mostly virtual analyst events in 2020*

	Compound	Indication	Milestone	
Phase III / pivotal readouts	**risdiplam**	SMA type 1	Ph II/III FIREFISH (part 2)	✓
	Tecentriq + Avastin	FL OC	Ph III IMagyn050	
	Tecentriq + chemo	Neoadjuvant TNBC	Ph III IMpassion031	
	Venclexta + azacitidine	1L unfit AML	Ph III Viale A	✓
	ipatasertib + chemo	Dx+ HR+ breast cancer	Ph III IPATunity130	
	ipatasertib + chemo	Dx+ 1L TNBC	Ph III IPATunity130	
	ipatasertib + abiraterone	1L mCRPC	Ph III IPATential150	
	PDS	nAMD	Ph III Archway	
	faricimab	DME	Ph III YOSEMITE/RHINE	
	etrolizumab	Ulcerative Colitis	Ph III HIBISCUS/LAUREL/HICKORY/GARDENIA	
	balovaptan	Autism spectrum disorders	Ph III V1aduct/Ph II aV1ation	**

Virtual Event on Digitalisation

Thursday, 7 May
15:00 to 16:30 CEST

ASCO IR Event (virtual)

Date to be confirmed

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

Roche Pharma Day

Monday, 14 September

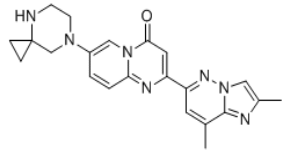
* Outcome studies are event-driven: timelines may change; ** Ph III in adults negative; Ph II in pediatrics ongoing

Neuroscience: Upcoming NME launches in 2020

Defining new standards of care in SMA and NMOSD

Risdiplam in SMA type 1/2/3

IR event today 28 April

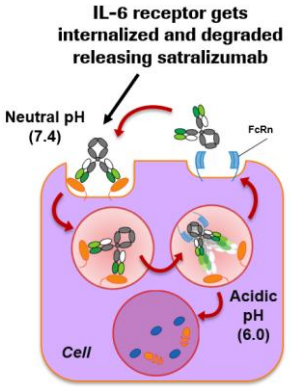


- Oral, systemically available SMN2 splicing modifier
- Durably increases SMN protein throughout the CNS and in peripheral tissues
- Excellent efficacy

- Positive Ph III (SUNFISH part 2) data in type 2 & 3 SMA ages 2 to 25 years presented in Q1
- Positive Ph III (FIREFISH part 2) in type 1 SMA presented at virtual event on 28 April
- US launch for types 1/2/3 expected in 2020;
  Priority review granted, PDUFA date set for August 24

Satralizumab in NMOSD

FDA BTD



- Recycling mAb with high-affinity to soluble and membrane-bound IL-6R
- Convenient SC Q4W dosing at home
- Well tolerated as monotherapy and in combination with immunosuppressants

- Robust efficacy, sustained for 144 weeks and with reduced risk of relapse across a broad patient population
- Clinically relevant population reflecting real world patients
- US/EU launch expected in 2H 2020

Risdiplam in collaboration with PTC Therapeutics and the SMA Foundation; NME=new molecular entity; SMA=spinal muscular atrophy; NMOSD=neuromyelitis optica spectrum disorder

FIREFISH Part 2: Efficacy and safety of risdiplam (RG7916) in infants with Type 1 spinal muscular atrophy (SMA)

Laurent Servais,[1–3*] Giovanni Baranello,[4,5] Riccardo Masson,[4] Maria Mazurkiewicz-Bełdzińska,[6] Kristy Rose,[7] Dmitry Vlodavets,[8] Hui Xiong,[9] Edmar Zanoteli,[10] Muna El-Khairi,[11] Sabine Fuerst-Recktenwald,[12] Marianne Gerber,[13] Ksenija Gorni,[14] Heidemarie Kletzl,[15] Renata Scalco,[12] Basil T. Darras[16] on behalf of the FIREFISH Working Group

[1]Division of Child Neurology, Centre de Références des Maladies Neuromusculaires, Department of Pediatrics, University Hospital Liège & University of Liège, Belgium; [2]MDUK Oxford Neuromuscular Center, Department of Paediatrics, University of Oxford, Oxford, UK; [3]I-Motion - Hôpital Armand Trousseau, Paris, France; [4]Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy; [5]The Dubowitz Neuromuscular Centre, NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health University College London, & Great Ormond Street Hospital Trust , London, UK;(current); [6]Department of Developmental Neurology, Medical University of Gdańsk, Gdańsk, Poland; [7]Paediatric Gait Analysis Service of New South Wales, The Children's Hospital at Westmead, Sydney, Australia; [8]Russian Children Neuromuscular Center, Veltischev Clinical Pediatric Research Institute of Pirogov Russian National Research Medical University, Moscow, Russia; [9]Department of Pediatrics, Peking University First Hospital, Beijing, China; [10]Department of Neurology, Hospital das Clínicas, University of São Paulo, São Paulo, Brazil; [11]Roche Products Ltd., Welwyn Garden City, UK; [12]Pharma Development Neurology, F. Hoffmann-La Roche Ltd., Basel, Switzerland; [13]Pharma Development, Safety, F. Hoffmann-La Roche Ltd, Basel, Switzerland; [14]PDMA Neuroscience and Rare Disease, F. Hoffmann-La Roche Ltd., Basel, Switzerland; [15]Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Basel, Switzerland; [16]Boston Children's Hospital, Harvard Medical School, Boston, MA, USA.

*Presenter

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Disclosures

- GB has received speaker and consultancy honoraria from AveXis, Inc., Roche, PTC, and Sarepta Therapeutics
- LS is a PI of SMA studies for Roche, Biogen, and AveXis; He has attended SAB of Biogen and AveXis and received consultancy fees from Biogen; He serves on the board for Cytokinetics
- RM is a PI of SMA studies for Roche, Avexis and Novartis and received consultancy fees from Biogen, Roche and Avexis
- MM-B has no disclosures
- KR is a PT Master Trainer and PT Advisory Board Member for Roche and Biogen. She also has an overarching consulting agreement with ATOM International who hold consulting agreements with: PTC Therapeutics, NS Pharma, Sarepta Therapeutics, Biomarin, QED, Acendis, Therachon, Catabasis, Italfarmaco, Santhera, Summit and Amicus. KR has no financial interest in any of these companies
- DV is a PI of SMA studies for F. Hoffmann-La Roche. He is also a PI for studies for PTC Therapeutics, Novartis, NS Pharma, Sarepta Therapeutics and Pfizer
- HX has not declared disclosures
- EZ is a PI of SMA studies for F. Hoffmann-La Roche
- BD is on advisory boards for AveXis, Biogen, Cytoknetics, PTC Therapeutics, Roche and Sarepta. He has received research support from the National Institutes of Health/National Institute of Neurological Disorders and Stroke, the Slaney Family Fund for SMA, Working on Walking Fund and the SMA Foundation; grants from CureSMA, Ionis Pharmaceuticals, Inc. and Biogen during ENDEAR, CHERISH, CS2, CS12, CS11 studies, Cytokinetics, Fibrogen, PTC, Roche, Santhera, Sarepta and Summit. BD has no financial interests in these companies
- HK, ME-K, MG, RS, SF-R and KG are current employees of F. Hoffmann-La Roche

DSMB, data and safety monitoring board; PI, Principal Investigator; SAB, scientific advisory board; SMA, spinal muscular atrophy.

Introduction

- Type 1 SMA is a severe, progressive neuromuscular disease, with untreated infants failing to achieve major motor milestones and typically dying before 2 years of age[1]
- Risdiplam (RG7916) is a centrally and peripherally distributed oral *SMN2* pre-mRNA splicing modifier that increases the levels of functional SMN protein[2,3]
- Here we present data for the first time from Part 2 of the FIREFISH trial in infants 1–7 months old* with Type 1 SMA who have received risdiplam for 12 months at the dose selected in Part 1
  - ➢ Primary endpoint, as well as additional motor milestone, survival and swallowing data will be presented

*At enrollment.
SMA, spinal muscular atrophy; SMN, survival of motor neuron.
1. Mercuri E, et al. Lancet Neurol. 2012; 11:443–452; 2. Ratni H, et al. J Med Chem. 2018; 61:6501–6517; 3. Poirier A, et al. Pharmacol Res Perspect. 2018; 6:e00447; 4. Clinicaltrials.gov. NCT02913482 (Accessed Mar 2020).

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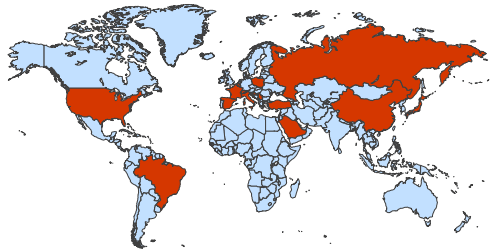
A multicenter, global, open-label study



12 Months

24 Months

Risdiplam → Risdiplam → Extension

Part 2[1]

N=41

Genetic diagnosis of 5q SMA symptomatic Type 1 SMA

Two *SMN2* gene copies

1–7 months old

Primary endpoint:

- **proportion of infants sitting without support for 5 seconds at Month 12 (as assessed by the Gross Motor Scale of the BSID-III)**

Key additional endpoints:

- time to death or permanent ventilation
- achievement of motor milestones at Month 12 as measured by the HINE-2
- proportion of infants who achieve an increase of ≥4 points in the CHOP-INTEND at Month 12
- proportion of infants who achieve a score of ≥40 in the CHOP-INTEND at Month 12
- ability to swallow and feed orally at Month 12
- number of nights in hospital per infant by Month 12

Safety of risdiplam

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; SMN, survival of motor neuron.

1. Clinicaltrials.gov. NCT02913482 (Accessed Mar 2020).

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Part 2 baseline characteristics are reflective of infants with symptomatic Type 1 SMA

	Risdiplam (N=41)
Age at enrollment, months, median (range)	5.3 (2.2–6.9)
Gender, n (%)	
Female	22 (54)
Male	19 (46)
Age at onset of symptoms, months, median (range)	1.5 (1.0–3.0)
Disease duration, months, median (range)	3.4 (1.0–6.0)
≤3 months, n (%)	14 (34)
>3 months, n (%)	27 (66)
CHOP-INTEND score, median (range)	22.0 (8.0–37.0)
HINE-2 score, median (range)	1.0 (0.0–5.0)

Data cut-off: 14 Nov 2019.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination, Module 2; SMA, spinal muscular atrophy.

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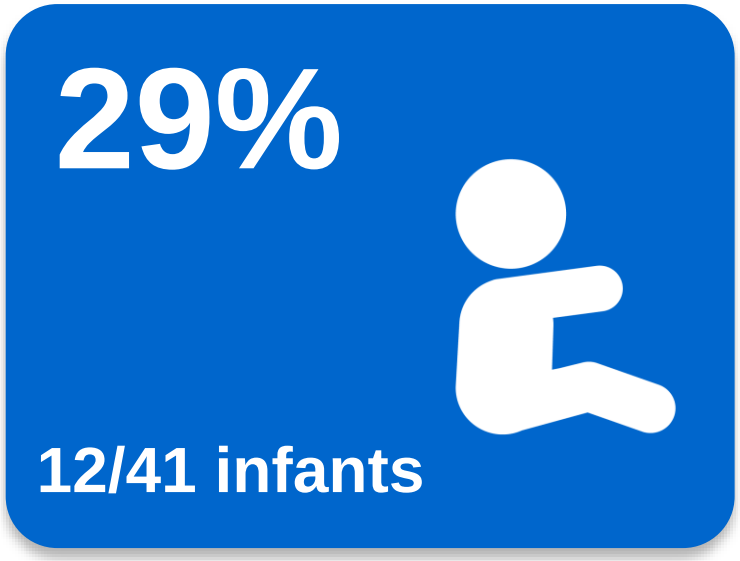
The study met its primary endpoint of the proportion of infants sitting at Month 12

Without treatment, children with Type 1 SMA are never able to sit without support[1]

Sitting without support for at least 5 seconds*



P<0.0001, performance criterion= 5%

*As assessed by item 22 of the BSID-III gross motor scale. Exact binomial test. Data cut-off: 14 Nov 2019.
BSID-III, Bayley Scales of Infant and Toddler Development, Third edition; SMA, spinal muscular atrophy.

1. Munsat T and Davies K. Neuromuscul Disord. 1992; 2:423–428.

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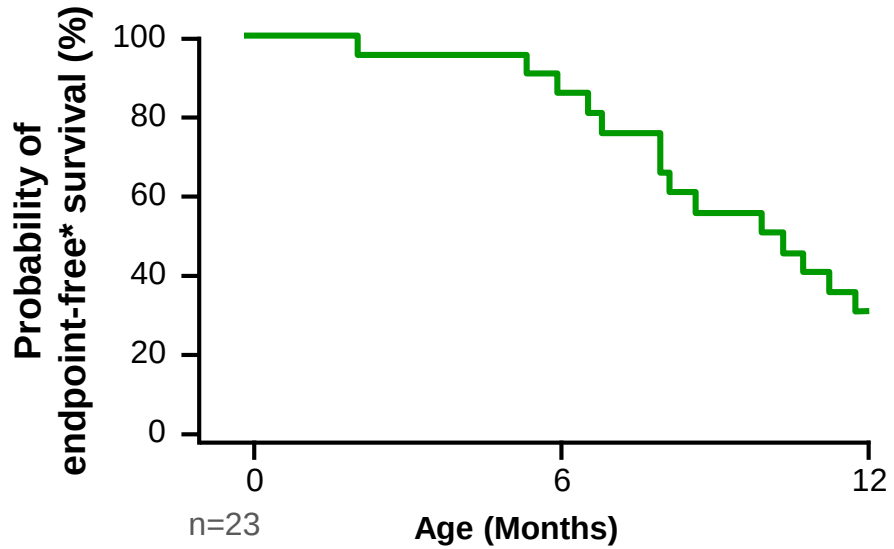
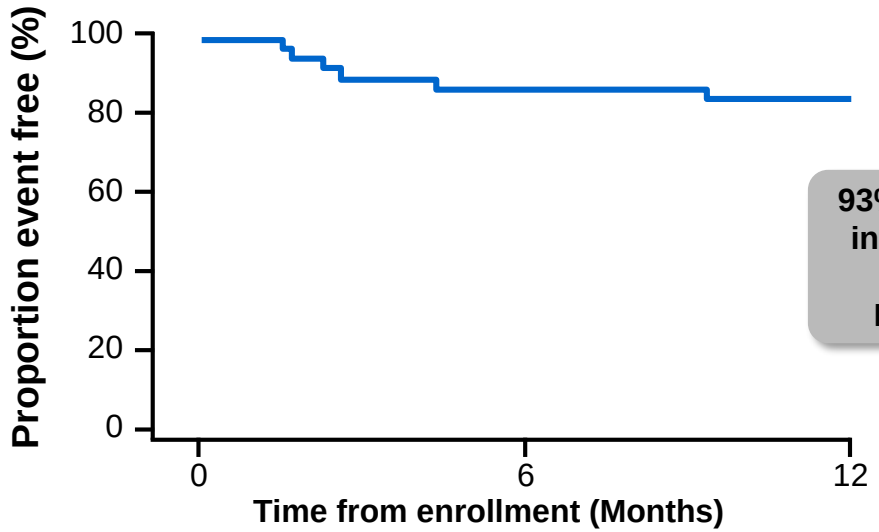
Event-free survival time was greatly improved in infants treated with risdiplam compared with natural history

Natural history data (PNCR) for infants with Type 1 SMA and two *SMN2* copies[1]



85% (35/41) of infants were event free† at Month 12 in FIREFISH Part 2‡



93% (38/41) of infants were alive at Month 12

Number of patients at risk

All patients	41	36	34§

In natural history, median age (IQR) for reaching death or permanent ventilation for infants with two *SMN2* copies was 10.5 (8.1–13.6) months[1]

In FIREFISH Part 2, median time to reaching death or permanent ventilation was not estimable due to lack of events

*Endpoint-free survival was defined as alive and not requiring at least 16 hours/day non-invasive ventilation support for at least 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). ‡Of the six infants who were not 'event-free', three infants met the definition of permanent ventilation and three had died. §One patient performed the Month 12 visit a few days early and therefore had not yet reached 12 months from enrollment as of the data cut-off. Data cut-off: 14 Nov 2019.

BiPAP. Bilevel Positive Airway Pressure; IQR, interquartile range; PNCR, Pediatric Neuromuscular Clinical Research Network; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Finkel R, et al. Neurology. 2014; 83:810–817.

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The HINE-2 scale measures motor function in infants

Absence of activity → **Normal activity**

Head control	Unable to maintain head upright	Wobbles	Maintain upright all the time		
Sitting	Cannot sit	With support at hips	Props	Stable sit	Pivots (rotates)
Voluntary grasp	No grasp	Uses whole hand	Index finger and thumb but immature grasp	Pincer grasp	
Ability to kick in supine	No kicking	Kicks horizontally but legs do not lift	Upward (vertically)	Touches leg	Touches toes
Rolling	No rolling	Rolling to side	Prone to supine	Supine to prone	
Crawling	Does not lift head	On elbow	On outstretched hand	Crawling flat on abdomen	Crawling on hands and knees
Standing	Does not support weight	Supports weight	Stands with support	Stands unaided	
Walking		Bouncing	Cruising (walks holding on)	Walking independently	

Used to assess posture, movements, tone and reflexes[1,2]

Items are scored from 0–4 (0=unable, 4=able)[2]

HINE-2, Hammersmith Infant Neurological Examination, Module 2.

1. Haataja L, et al. J Pediatrics. 1999; 135:153–161; 2. De Sanctis R, et al. Neuromuscul Disord. 2016; 26:754–759.

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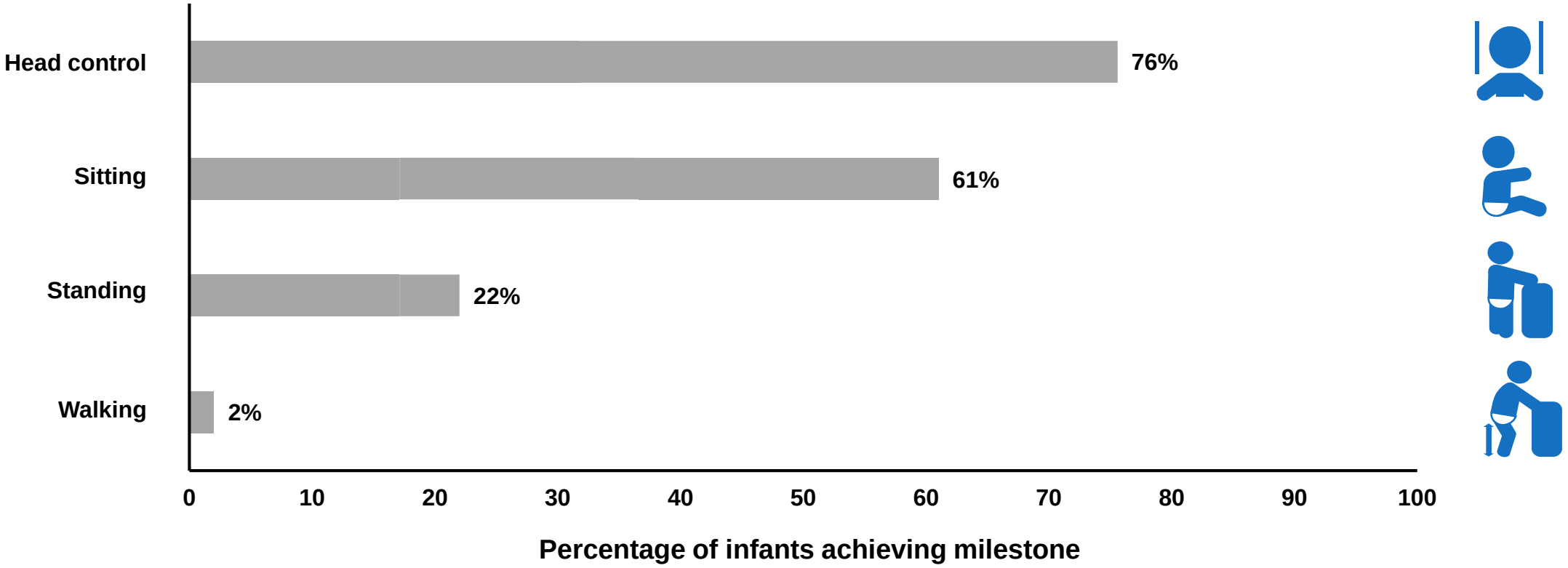
Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



78% of infants (32/41) responded to treatment using the HINE-2 scale and pre-specified response criteria*†

*Infant classed as responder if more motor milestones show improvement than show worsening. Improvement defined as a ≥2-point increase in ability to kick (or maximal score) or ≥1-point increase in head control, rolling, sitting, crawling, standing or walking. Worsening defined as ≥2-point decrease in ability to kick (or lowest score) or ≥1-point decrease in head control, rolling, sitting, crawling, standing or walking. †P<0.0001, performance criterion=12%, exact binomial test. Data cut-off: 14 Nov 2019.
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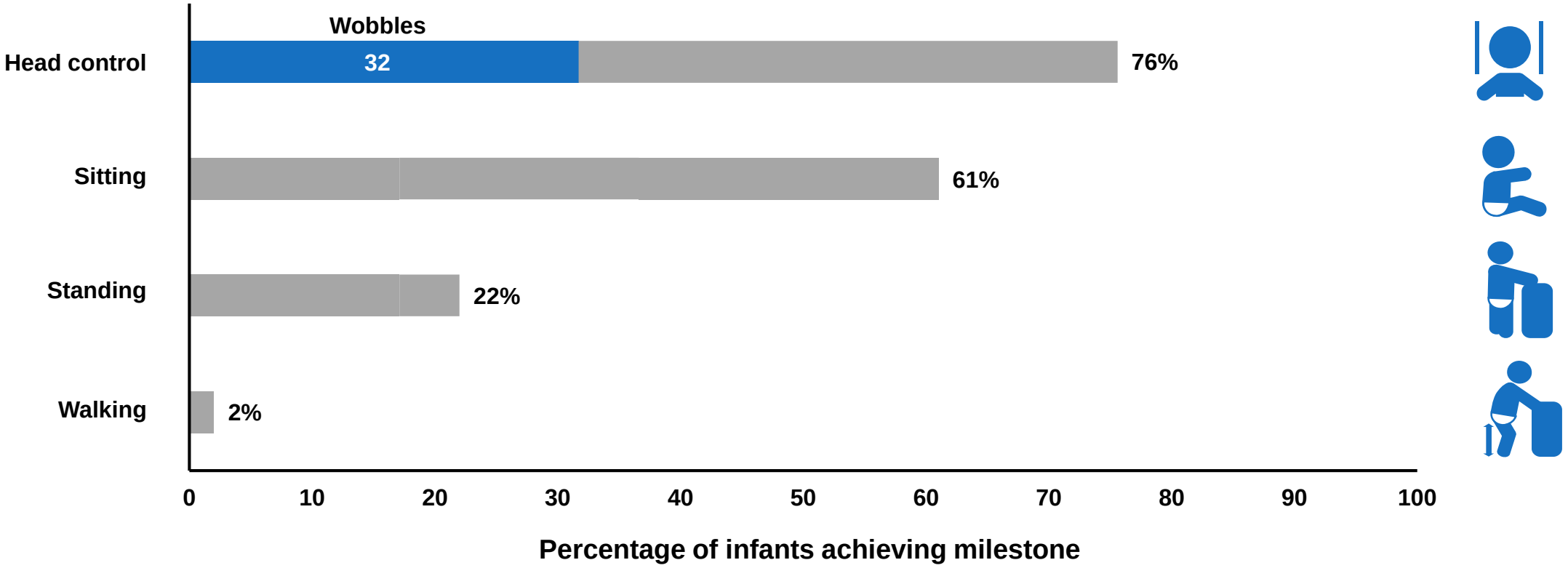

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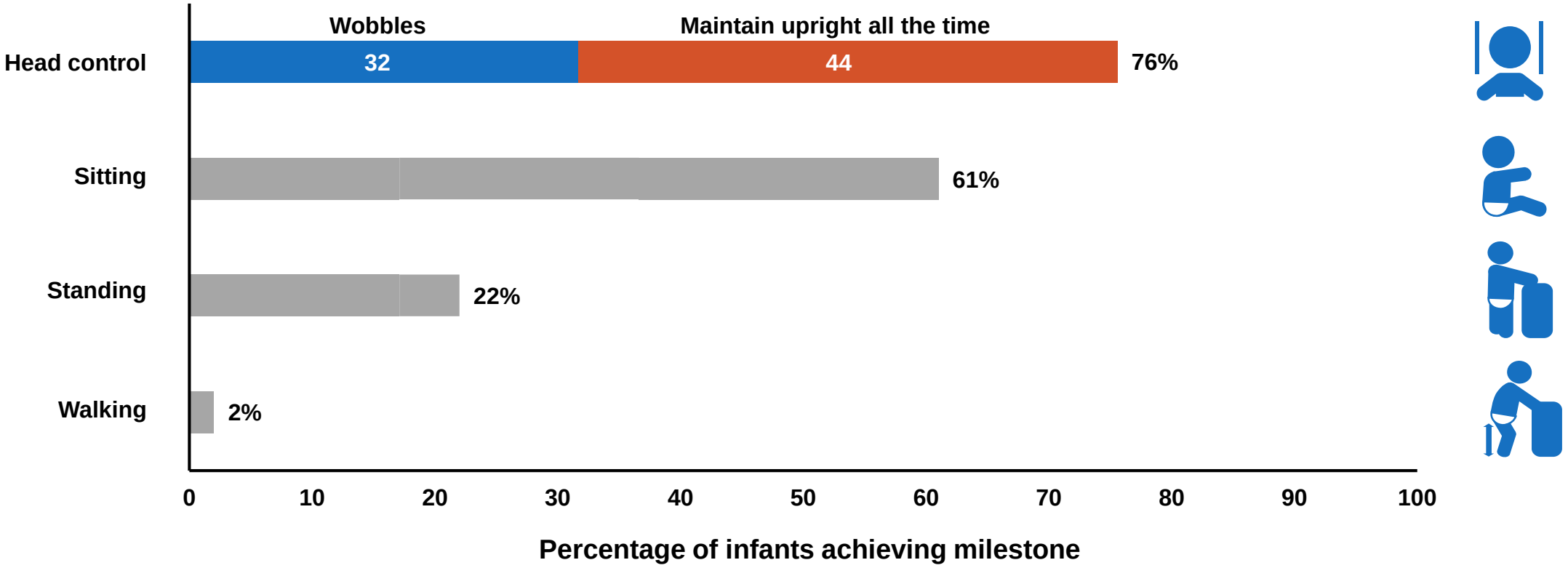

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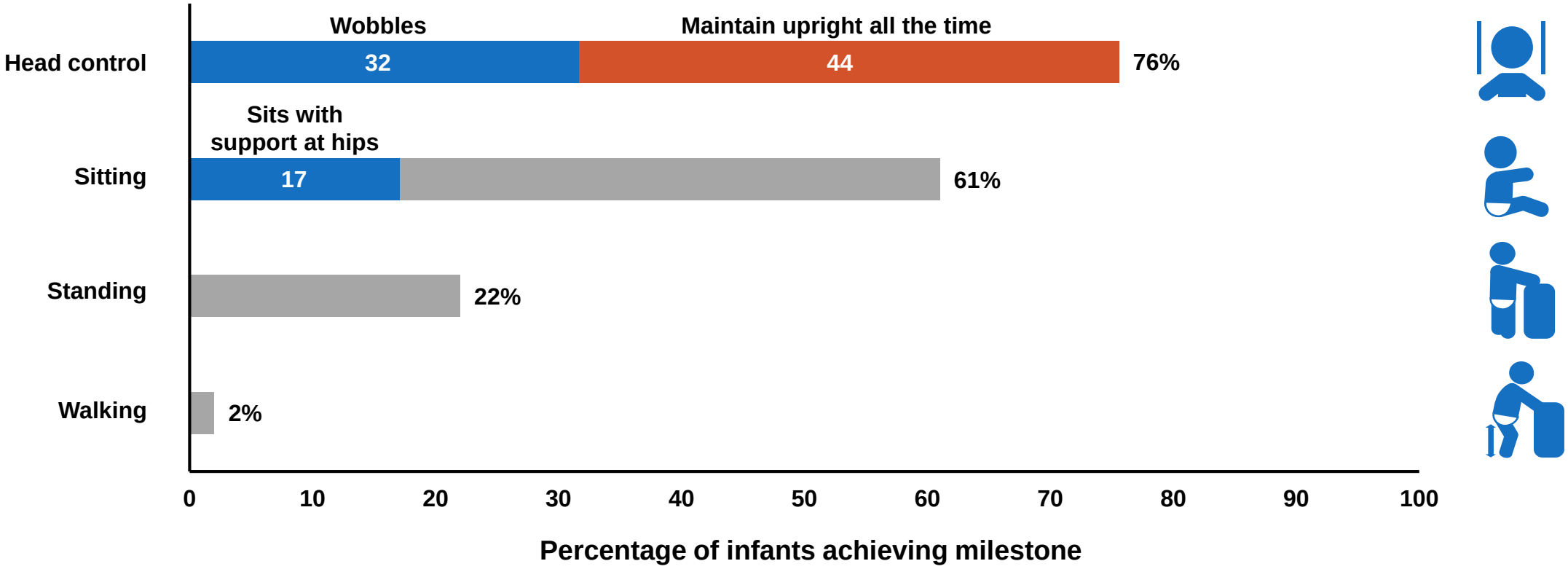

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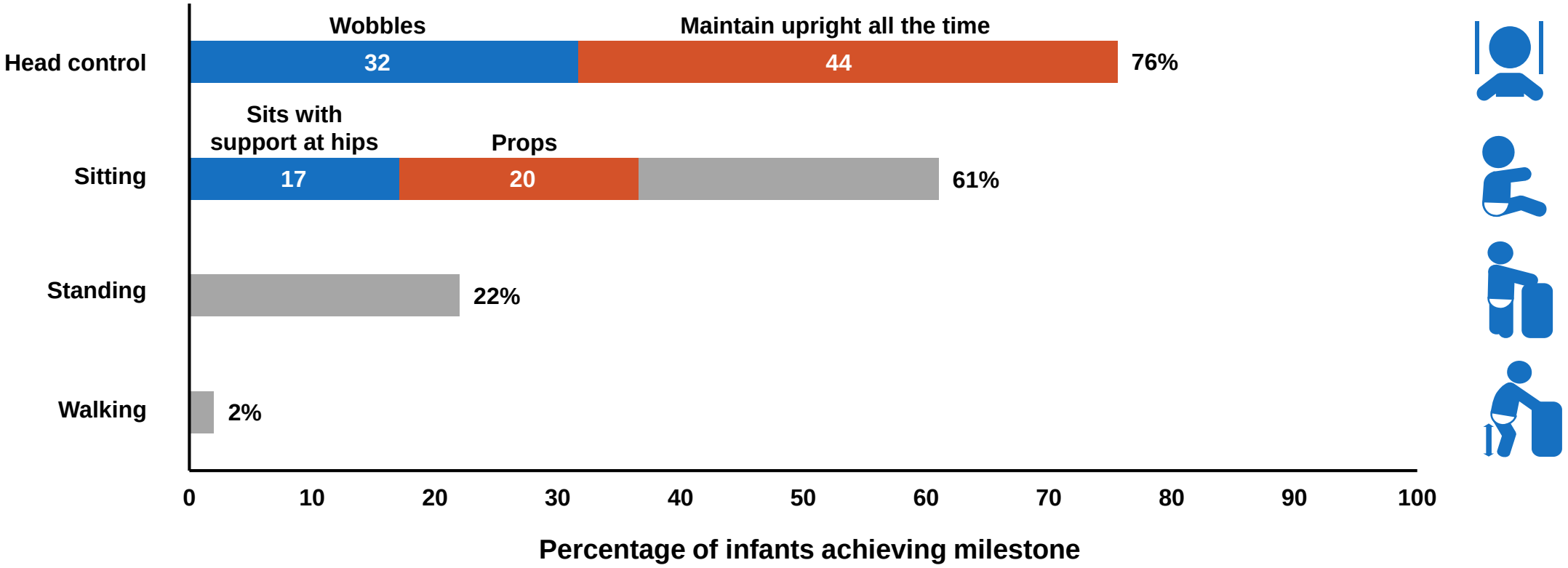

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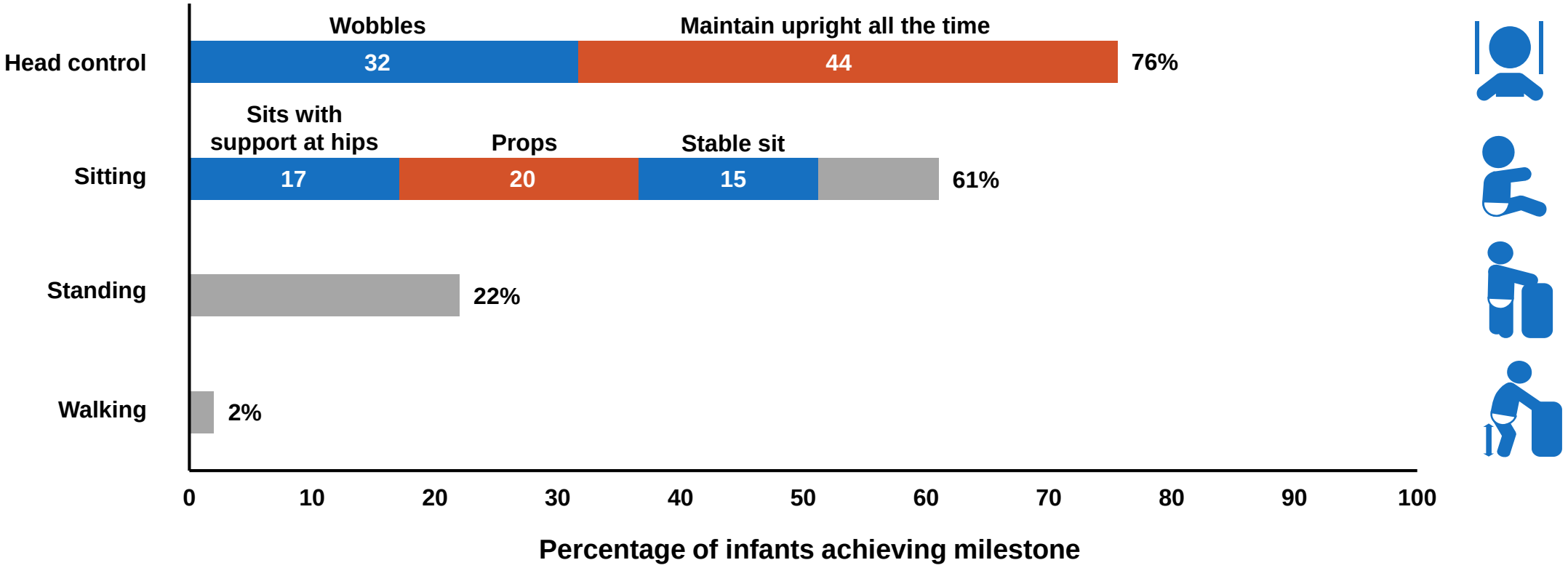

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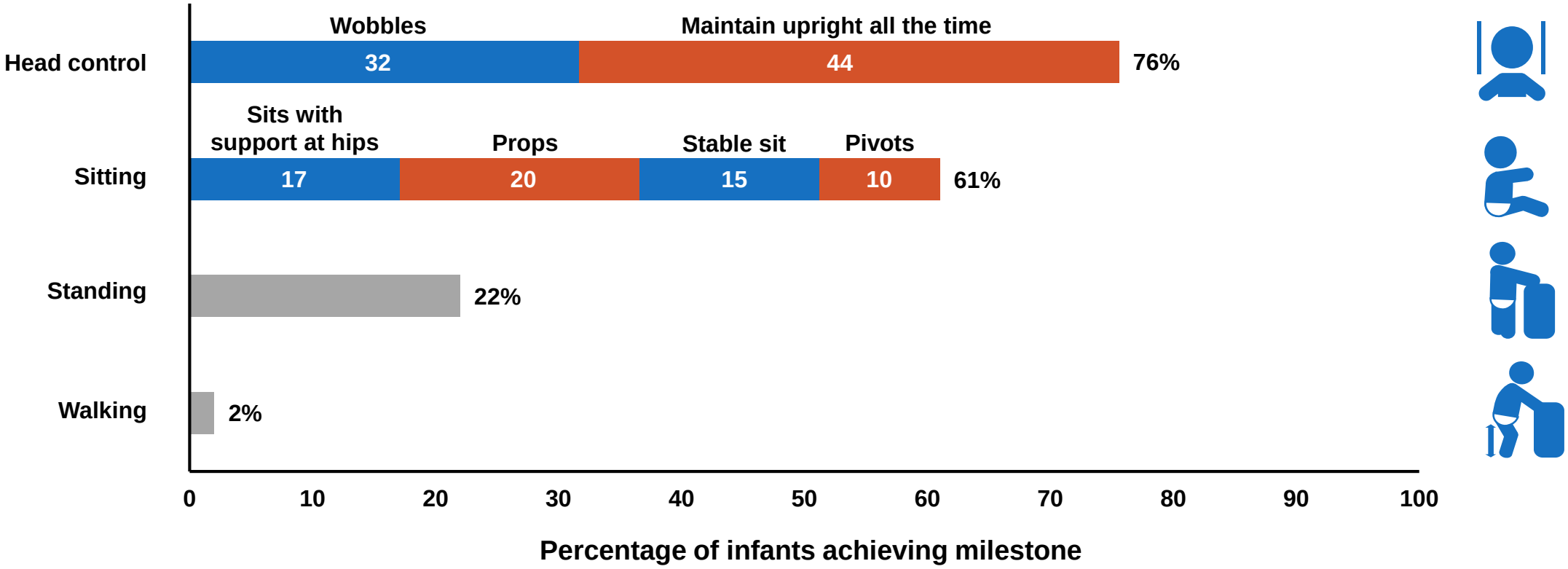

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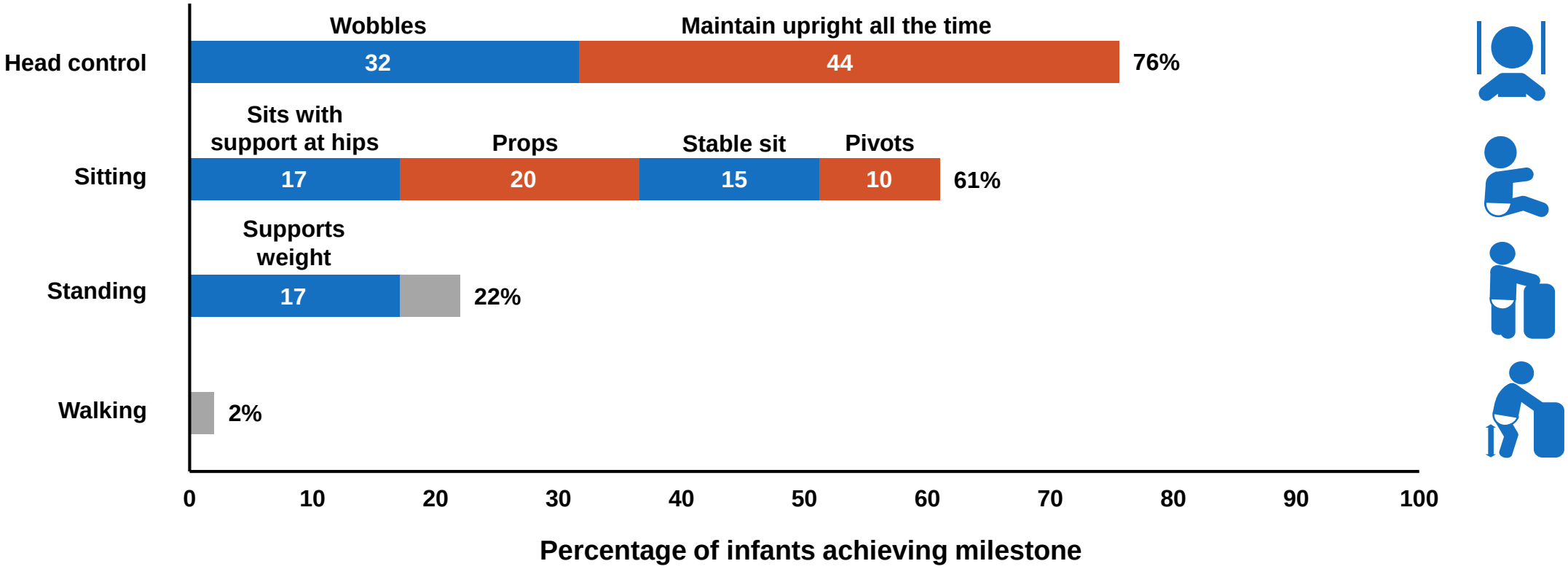

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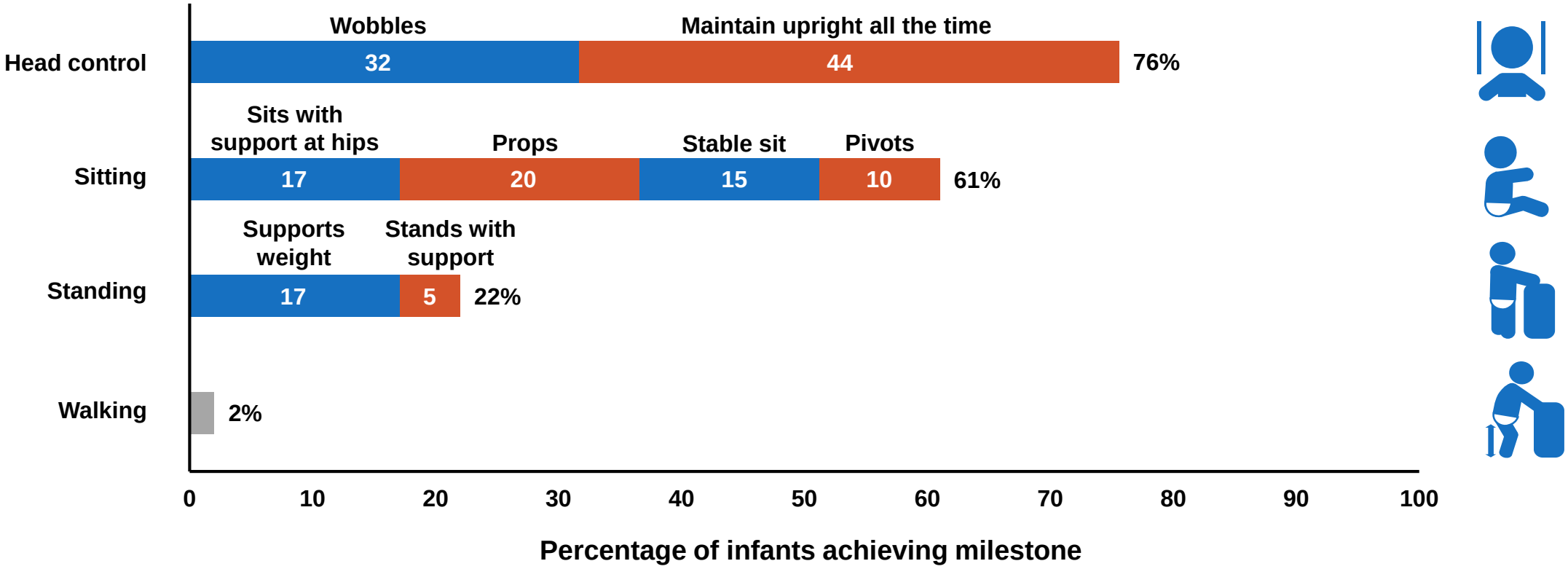

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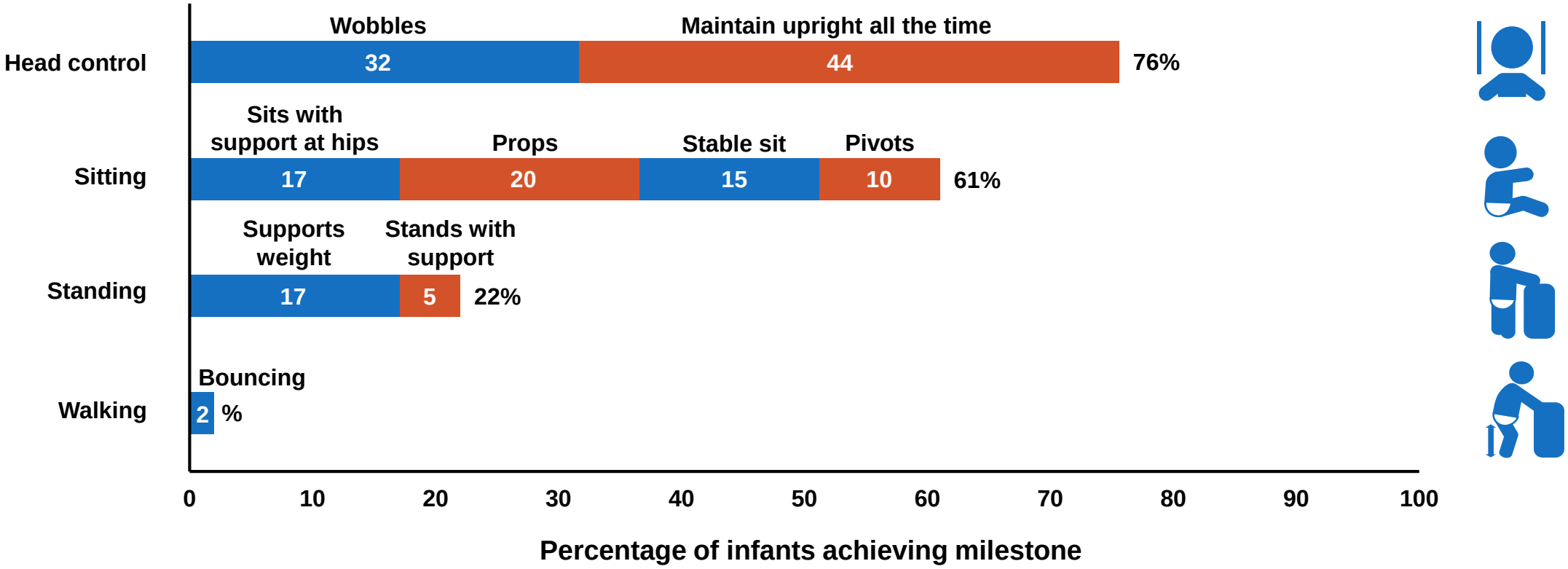
*Infant classed as responder if more motor milestones show improvement than show worsening. Improvement defined as a ≥2-point increase in ability to kick (or maximal score) or ≥1-point increase in head control, rolling, sitting, crawling, standing or walking. Worsening defined as ≥2-point decrease in ability to kick (or lowest score) or ≥1-point decrease in head control, rolling, sitting, crawling, standing or walking. †P<0.0001, performance criterion=12%, exact binomial test. Data cut-off: 14 Nov 2019.
HINE-2, Hammersmith Infant Neurological Examination, Module 2.

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

Risdiplam treatment resulted in significant gains in motor milestones after 12 months (HINE-2 items)



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HINE-2, Hammersmith Infant Neurological Examination, Module 2.

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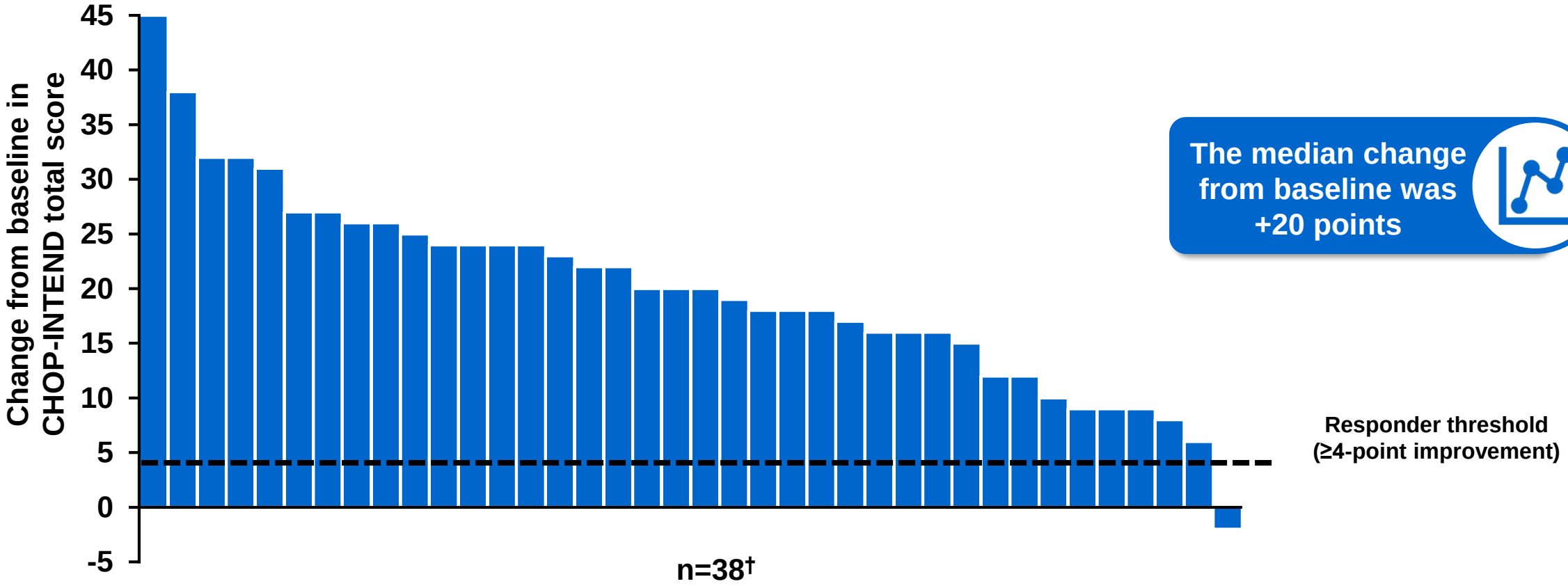
90% (37/41) of infants achieved an increase of ≥4 points in CHOP-INTEND total score at Month 12*

Without treatment, infants with Type 1 SMA show a steady decline in CHOP-INTEND scores over time[1]



*P<0.0001, performance criterion=17%, exact binomial test. †Change in CHOP-INTEND at Month 12 individual patient data available for n=38 infants due to 3 infant deaths. Data cut-off: 14 Nov 2019.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; SMA, spinal muscular atrophy.
1. Finkel RS, et al. Neurology. 2014; 83:810–817.

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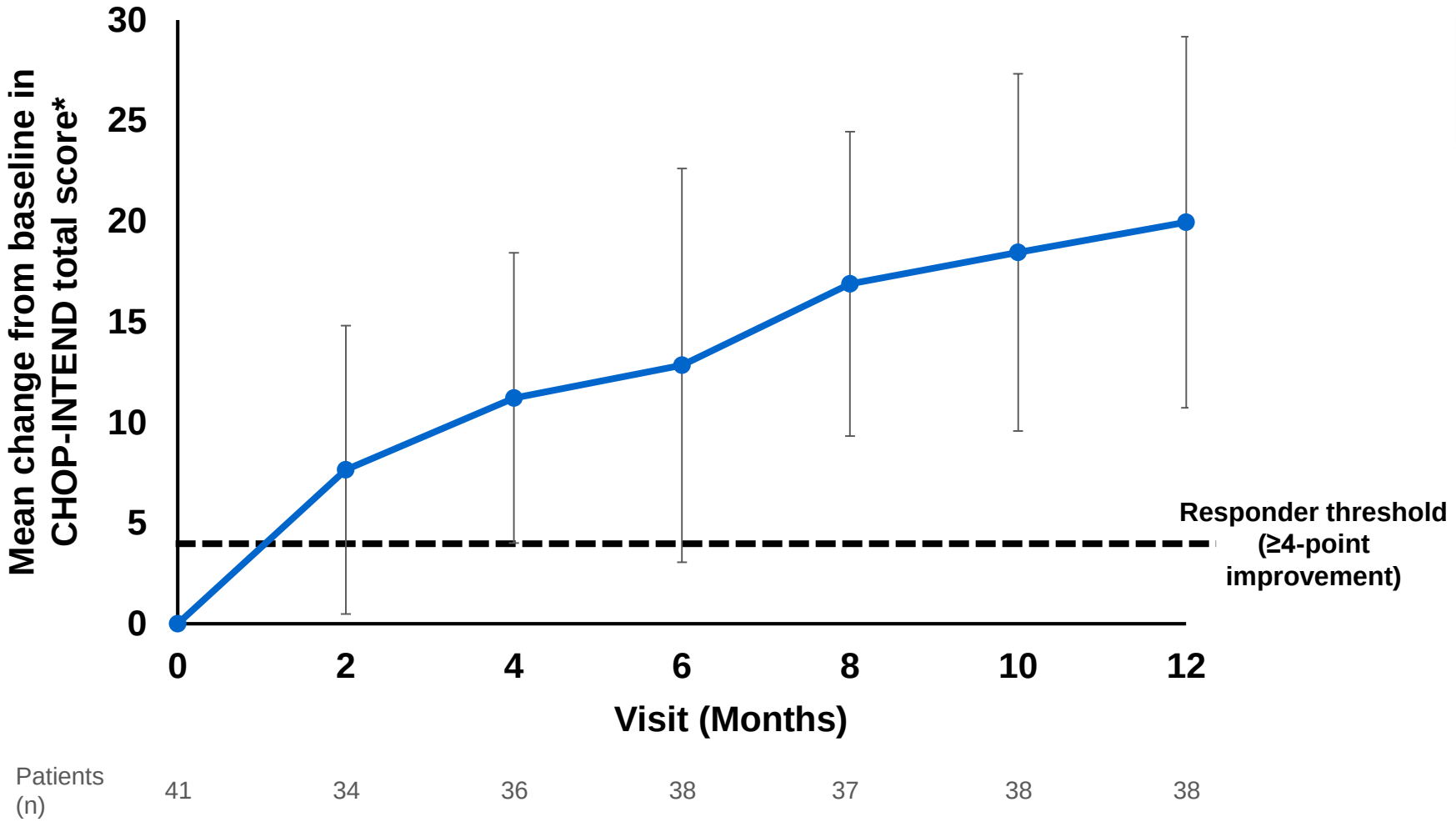
CHOP-INTEND total score continued to improve over 12 months



In natural history, children with Type 1 SMA rarely reach a CHOP-INTEND total score of 40 points[1]

56% (23/41) achieved a CHOP-INTEND score ≥40 at Month 12† in FIREFISH Part 2

*±Standard deviation. †P<0.0001, performance criterion=17%, exact binomial test. Data cut-off: 14 Nov 2019.
CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders.

1. Finkel R, et al. Neurology. 2014; 83:810–817.

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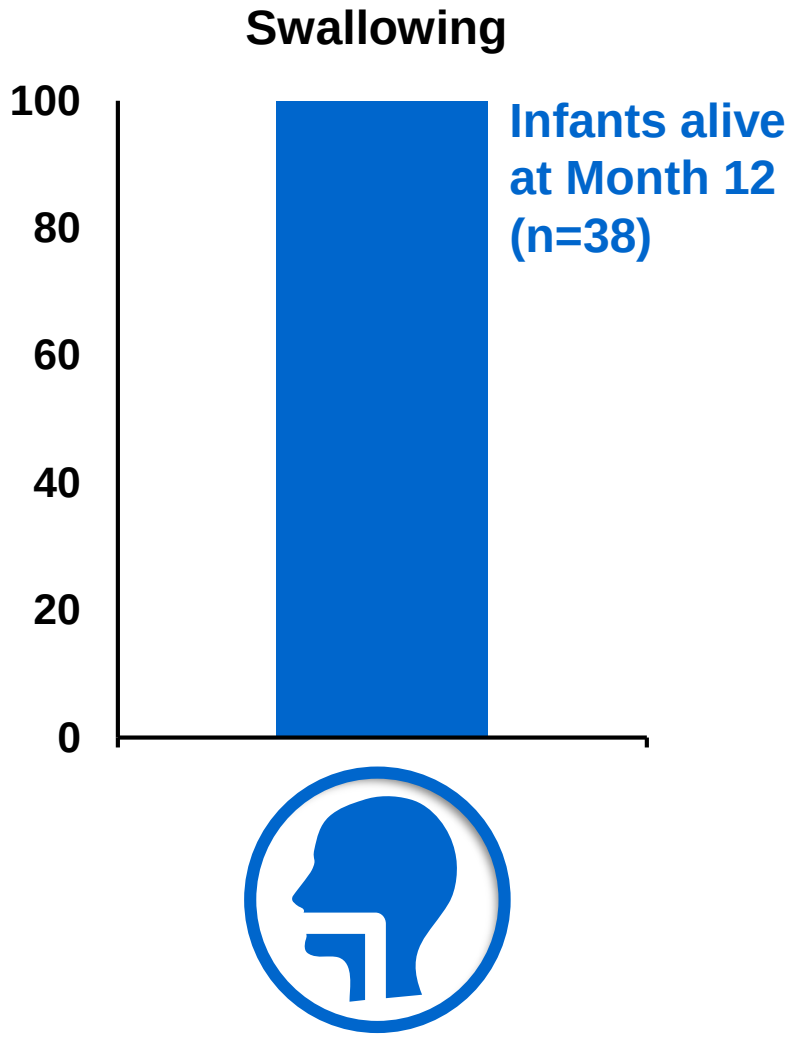
Swallowing and feeding ability was maintained by the majority of infants alive at Month 12



Data cut-off: 14 Nov 2019.

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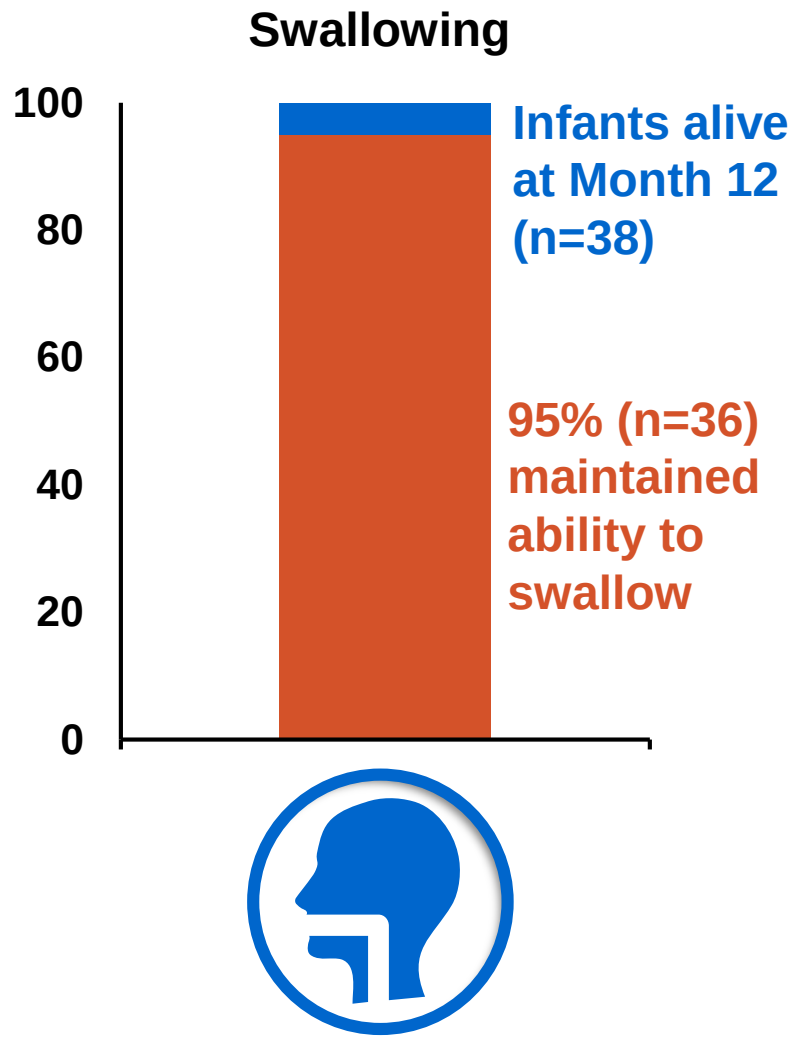

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

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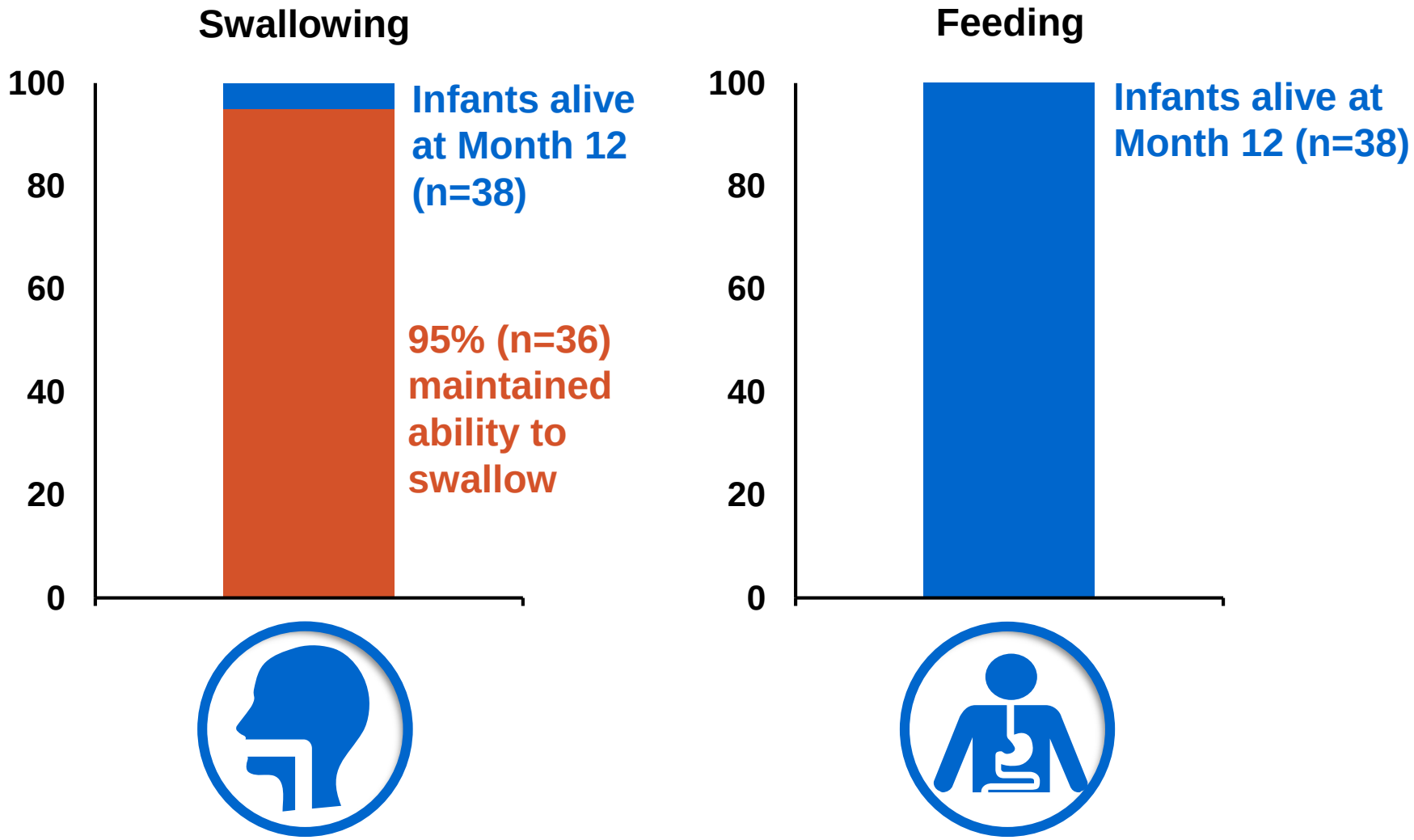

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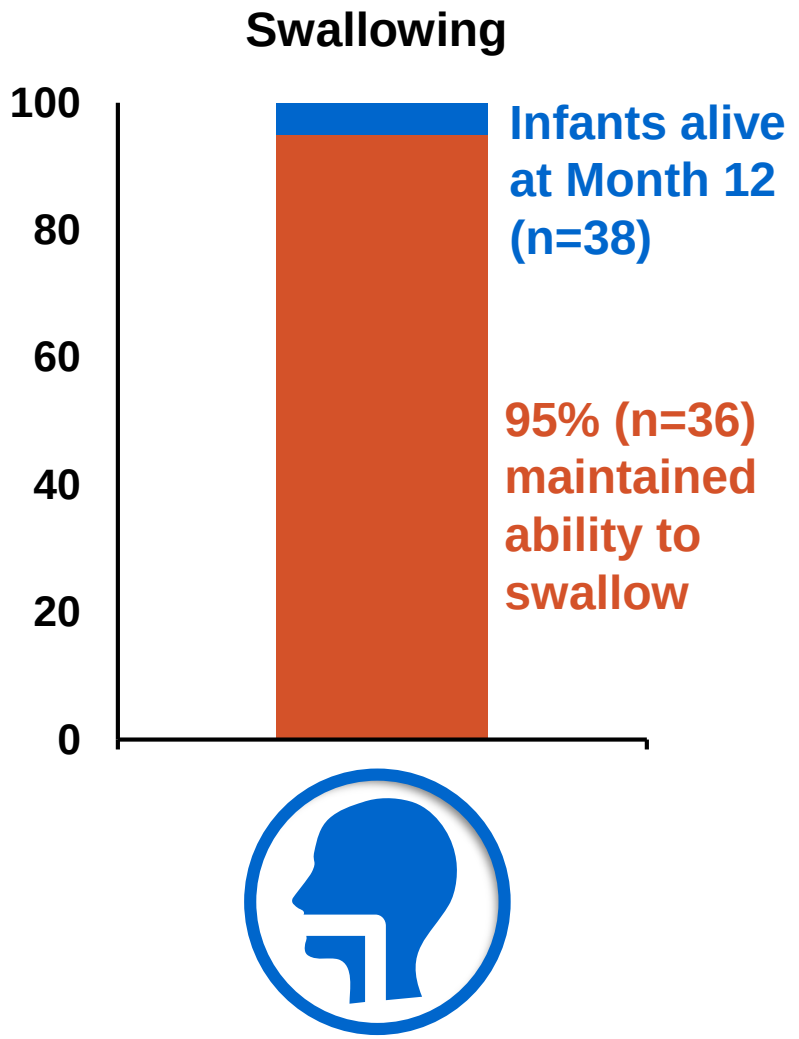

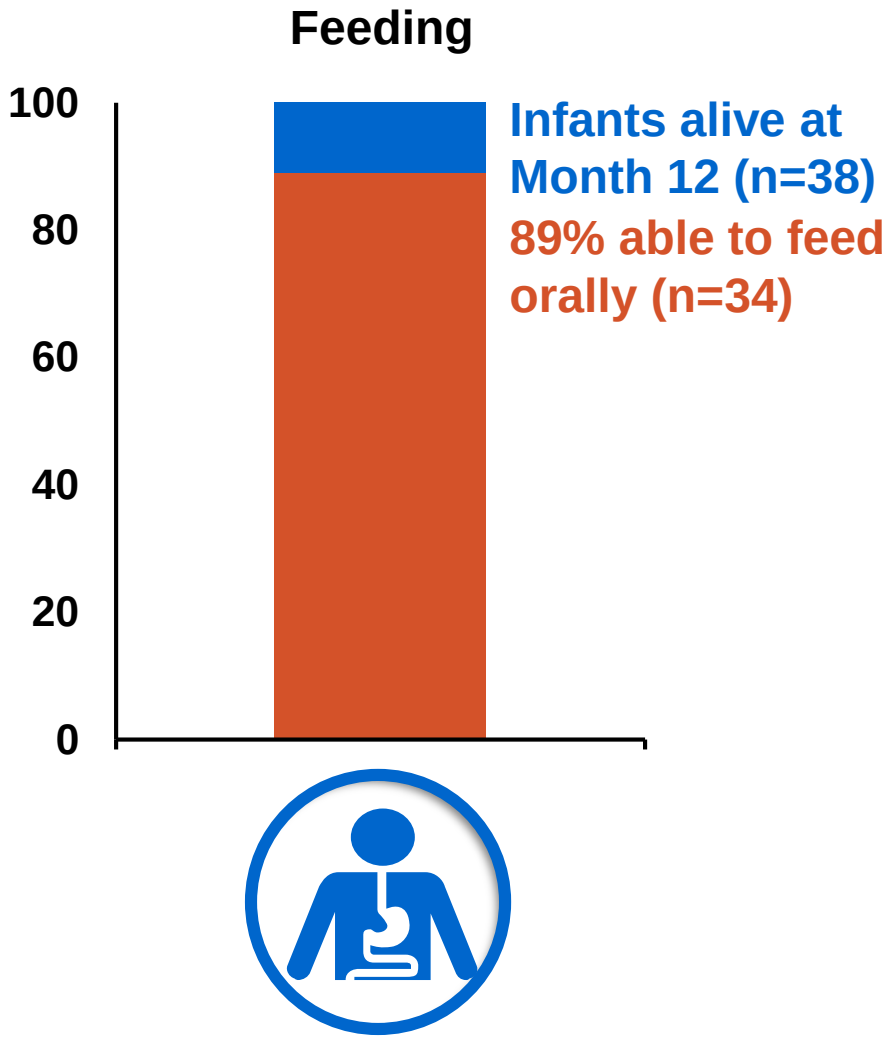

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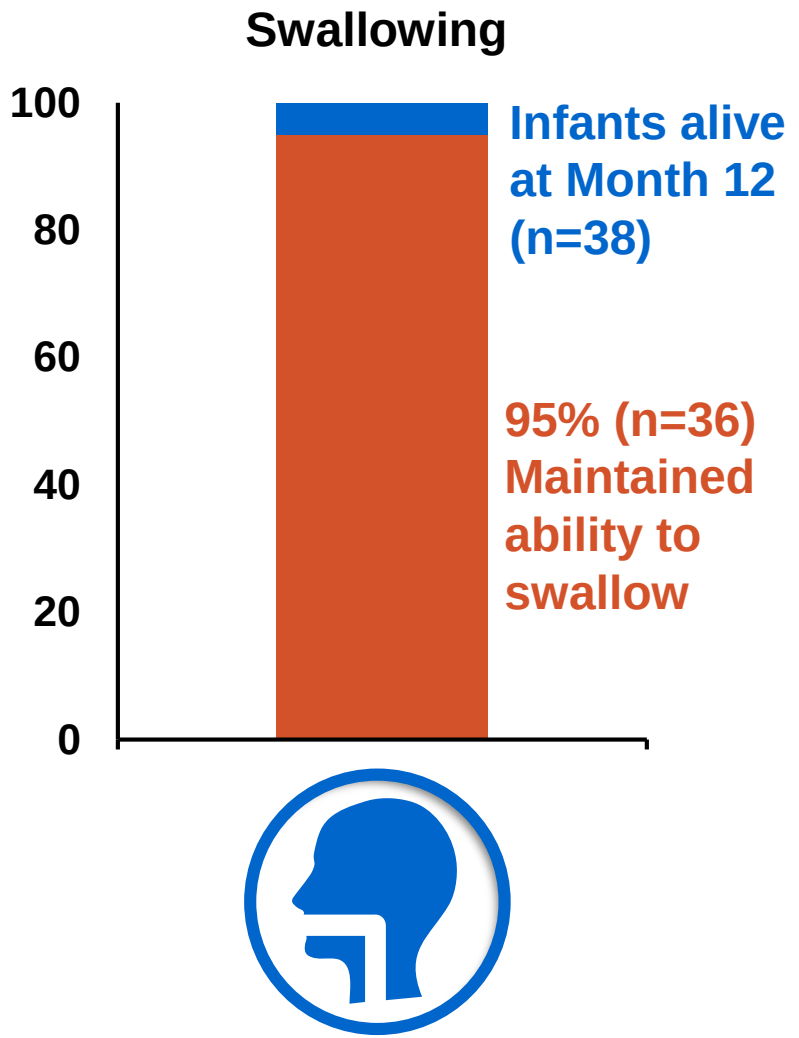
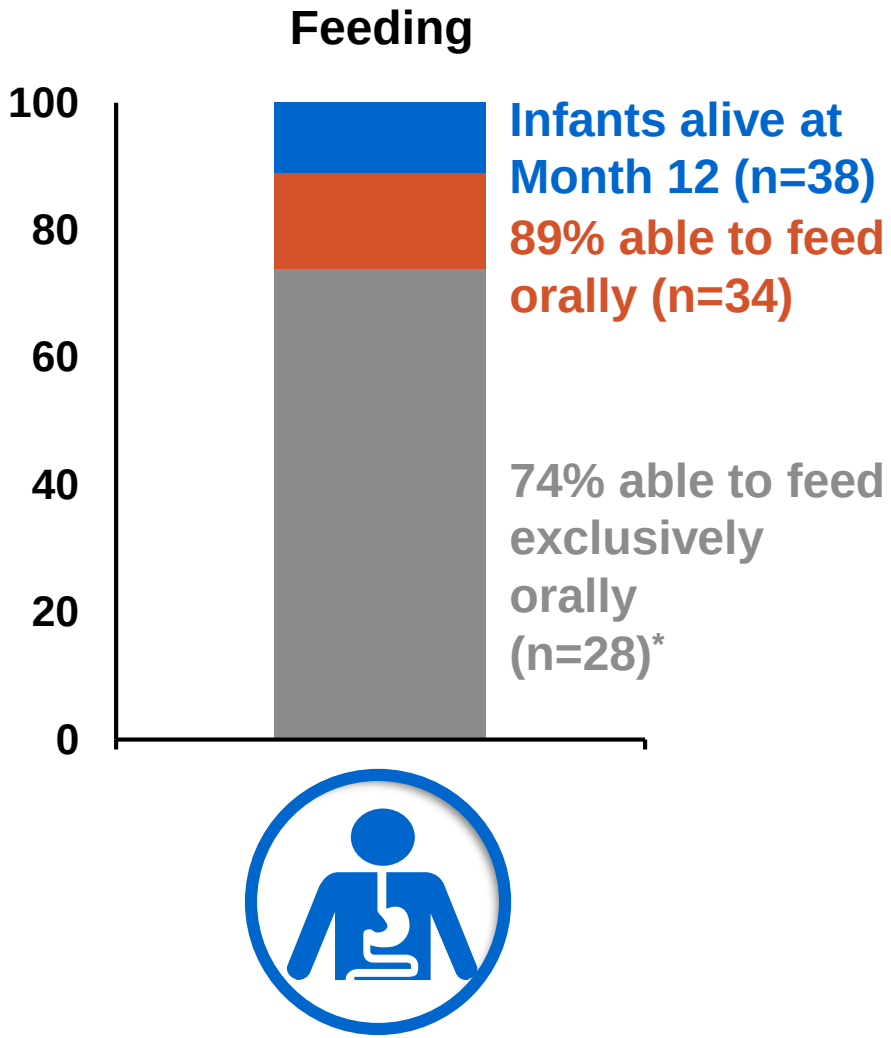




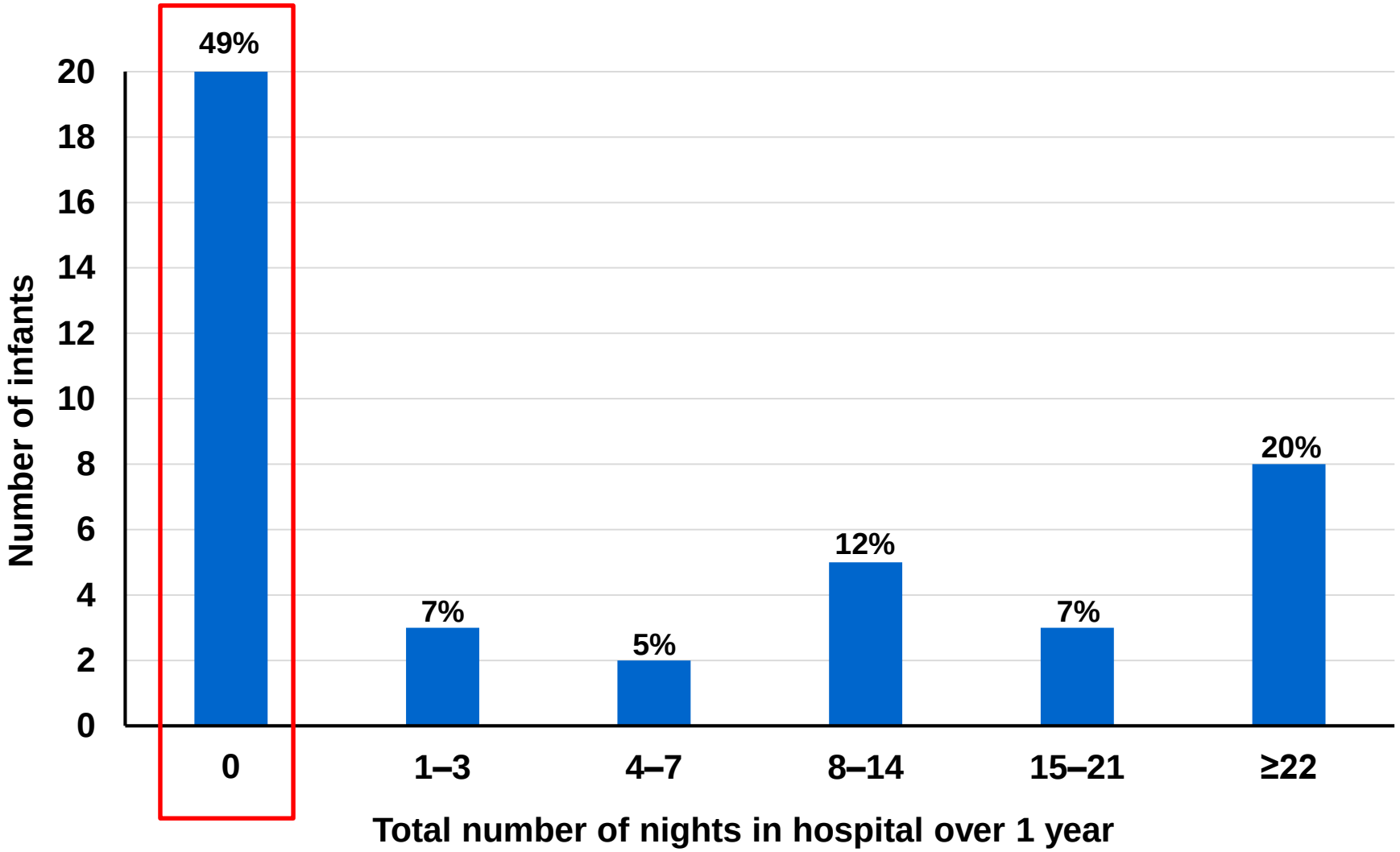
In a natural history cohort, all infants with Type 1 SMA older than 12 months required feeding support[1]

*Six infants fed orally in combination with a feeding tube and four fed exclusively via a feeding tube. Data cut-off: 14 Nov 2019.
SMA, spinal muscular atrophy.

1. Finkel RS, et al. Neurology. 2014; 83:810–817.

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

Nearly half of all infants (49%, 20/41) did not require hospitalization up to Month 12*



In natural history, children with Type 1 SMA experienced between ~4.2 and 7.6 hospitalizations every year[1,2]

There were 1.30 hospitalizations per patient-year in FIREFISH Part 2 (90% CI: 1.02, 1.65)

*Hospitalizations include hospital admissions ≥1 night. Data cut-off: 14 Nov 2019.
SMA, spinal muscular atrophy.
1. Shieh PB, et al. Presented at CureSMA 2017; 2. Chatwin M, et al. Arch Dis Child 20011; 96:426–432.

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There have been no drug-related AEs leading to withdrawal or treatment discontinuation*

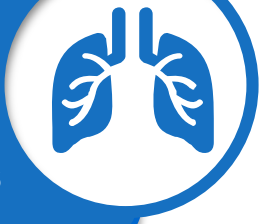
		Risdiplam (n=41)
Patients with at least one AE, n (%)		41 (100)
Total number of AEs		254
Total number of deaths, n (%)		3 (7)
Total number of patients with at least one AE, n (%)	AE with fatal outcome†	3 (7)
	SAE	24 (59)
	SAE leading to withdrawal from treatment	0
	SAE leading to dose modification/interruption	1 (2)
	Treatment-related SAE	0
	AE leading to withdrawal from treatment	0
	AE leading to dose modification/interruption	2 (5)
	Treatment-related AE	7 (17)
	Related AE leading to withdrawal from treatment	0
	Related AE leading to dose modification/interruption	0
	Grade 3–5 AE	22 (54)

*Up to data cut-off: 14 Nov 2019. †Fatal events were reported in three infants: (1) Pneumonia with fatal outcome on study Day 51 in male infant aged 4.5 months at first dose; (2) Acute respiratory failure on study Day 68 in male infant aged 6.9 months at first dose, related to Type 1 SMA and medical history or concurrent illness (thoracic cage deformity, probably infection); (3) Pneumonia with fatal outcome on study Day 79 in male infant aged 4.6 months at first dose. Events reported as unrelated to risdiplam and secondary to SMA-related respiratory complications.
AE, adverse event; SAE, serious AE; SMA, spinal muscular atrophy.

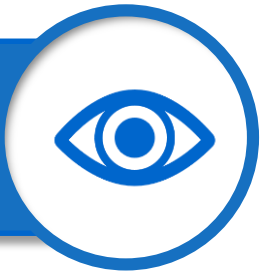
AEs and SAEs were reflective of underlying disease*

		Risdiplam (n=41)
Most common AEs, ≥4 patients, n (number of patients [%])	Upper respiratory tract infection	19 (46)
	Pneumonia	16 (39)
	Pyrexia	16 (39)
	Constipation	8 (20)
	Nasopharyngitis	5 (12)
	Rhinitis	5 (12)
	Diarrhea	4 (10)
	Rash maculo-papular	4 (10)
Most common SAEs, ≥2 patients, n (number of patients [%])	Pneumonia	13 (32)
	Bronchiolitis	2 (5)
	Respiratory failure	2 (5)
	Hypotonia	2 (5)

The incidence of serious pneumonia declined by approximately half between first and second 6-month periods



No risdiplam-associated ophthalmologic findings were observed



- **The most frequent AE was upper respiratory tract infection**
- **The most common SAE was pneumonia**
- **Skin events were non-serious and resolved with ongoing treatment**

*Up to data cut-off: 14 Nov 2019.
AE, adverse event; SAE, serious AE; SMA, spinal muscular atrophy.

Conclusions from FIREFISH Part 2 at 12 months

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

*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.

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Acknowledgments

Many thanks to all the patients who participate in these studies and their families, healthcare professionals and the support of patient groups throughout the world

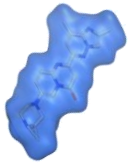
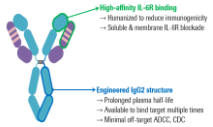
Risdiplam: Update on clinical development program in patients with Type 1, 2 & 3 SMA

OCREVUS: Long-term disability progression and thalamic atrophy data in MS
Shorter infusion (ENSEMBLE PLUS) data and regulatory update

Paulo Fontoura, M.D. Ph.D.
Global Head Neuroscience and Rare Diseases Clinical Development

Pushing towards new frontiers in Neuroscience

Creating new opportunities across modalities

Neuroimmunology	Neuromuscular	Neurodegenerative	Neurodevelopmental
Ocrevus *First B-cell targeted therapy in MS* 	**risdiplam** *First oral therapy for spinal muscular atrophy* 	**HTT-ASO**  *First disease modifying therapy for Huntington's disease*	**balovaptan** *First treatment for core social and communication deficits in Autism* 
Enspryng (satralizumab) *BTD in NMOSD* 	**SRP-9001** (Sarepta) *Gene therapy in Duchene Muscular Dystrophy*	**prasinezumab** *First disease modifying agent in Parkinsons* 	
		gantenerumab *First disease modifying therapy for Alzheimer Disease, SC convenience*	

NMOSD=neuromyelitis optica spectrum disorder

SAkuraStar, the monotherapy study of satralizumab in patients with NMOSD is now published in *Lancet Neurology*

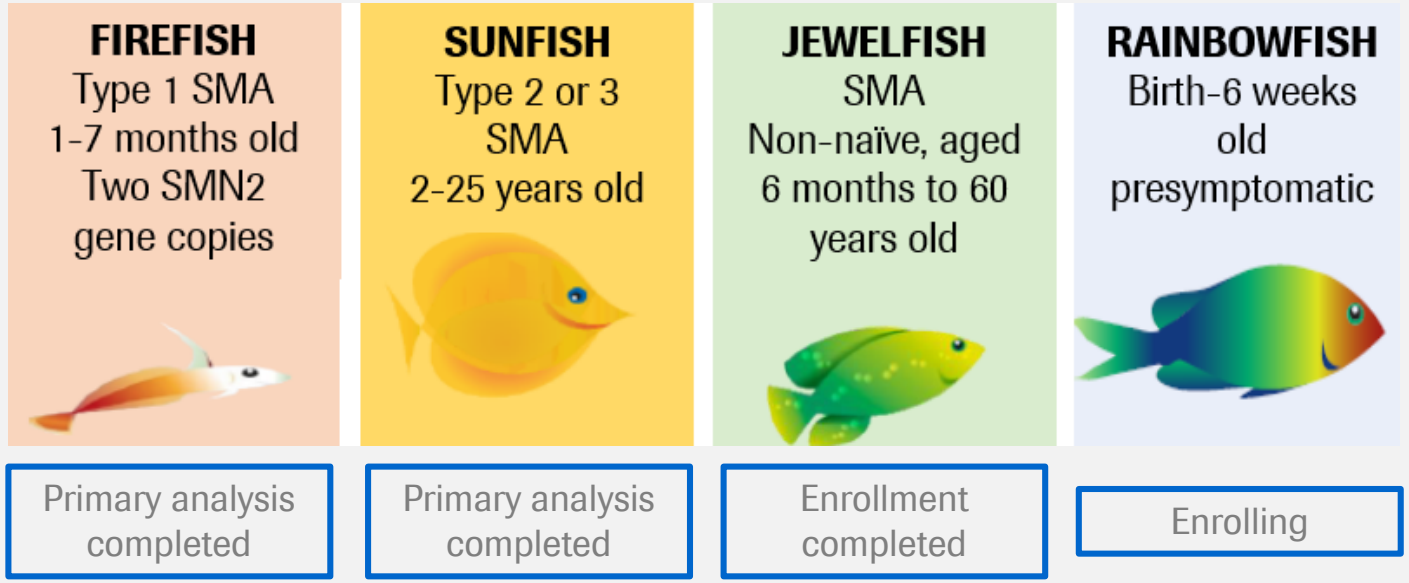
- **SAkuraStar validates results of SAkuraSky, the satralizumab combination study with baseline immunosuppressants, published in NEJM, and verifies the driving role of IL-6 in NMOSD**
- **Launch in US/EU in 2H 2020 on track**

Risdiplam in spinal muscular atrophy (SMA)

Compelling benefit/risk profile in infants, children, teenagers, and adults

- Durably increases SMN protein throughout the CNS and in peripheral tissues
- Positive efficacy in Type 1 infants (n=62 total)
- Positive efficacy in large (n=180) placebo-controlled study in a broad spectrum of Type 2/3 patients
- Consistent safety profile across trials
- No treatment-related safety findings have led to withdrawal in any study

Over 450 patients treated with risdiplam to date



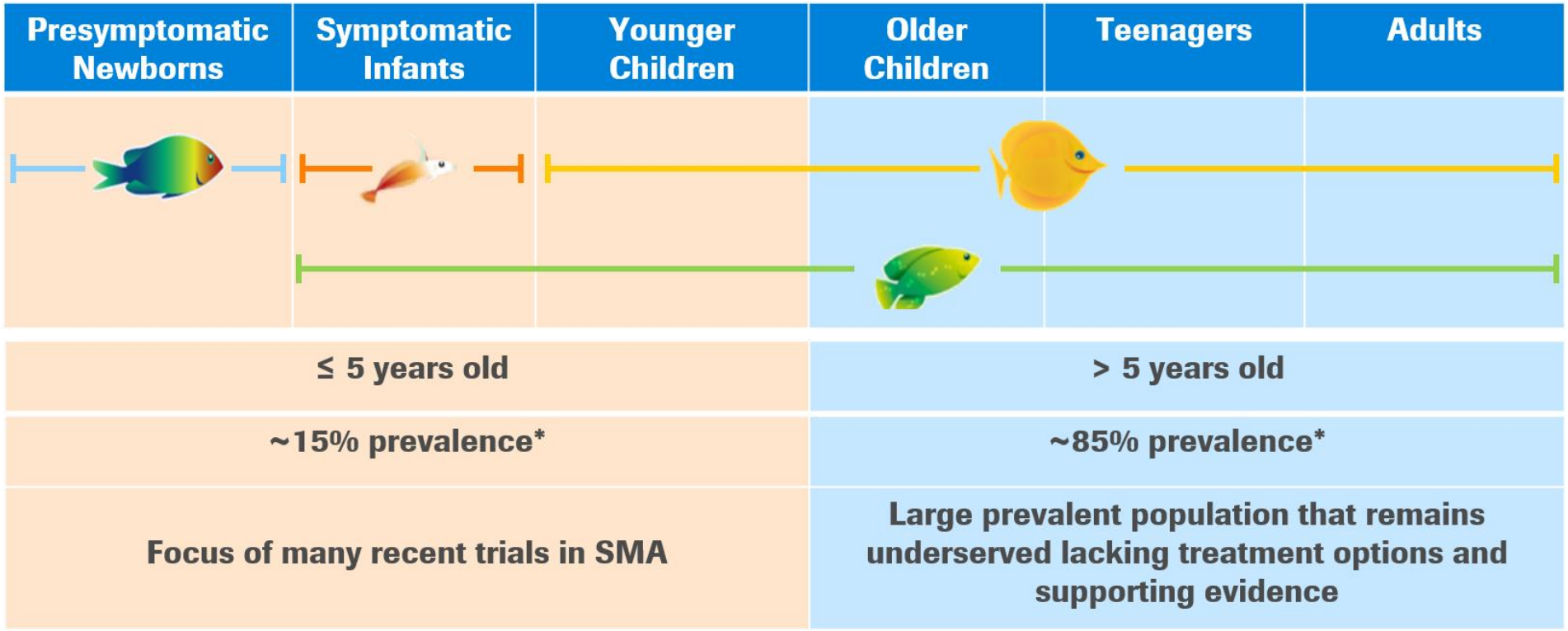
Potential to be the treatment of choice for a majority of patients living with SMA

Risdiplam program is a collaboration with PTC Therapeutics and the SMA Foundation

Meaningful evidence being generated across a broad program

Overview of the risdiplam development program

- Spanning types 1, 2, & 3 SMA; naïve and pre-treated
- Newborns to 60 years old; randomized, placebo-controlled data in 2 – 25 years old
- Including real-world spectrum of SMA – scoliosis, joint contractures, low baseline motor scale scores, etc.

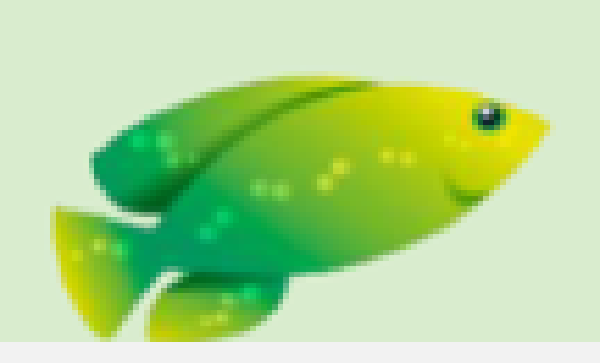


* Estimated 2020 prevalence in US and EU5

JEWELFISH update

Large open-label study of non-naïve patients completed enrollment

Prior SMA therapy	n
Olesoxime	74
Spinraza	73
AVXS-101	14
RG7800	13
TOTAL	**174**



- **Primary objectives**: safety/tolerability and PK/PD
- Poster prepared for AAN 2020
  - Preliminary safety data from 45 patients (6 mo to 60 yrs) who had received risdiplam for up to 28.9 months
  - No drug-related AEs leading to withdrawal
  - Overall safety profile consistent with patients who have not received previous treatment
- Exploratory efficacy to be reported after 1 year of follow-up (2021)
- Data collected on reasons for switching therapy (to be presented later in 2020)

Regulatory procedures moving at pace around the globe

- 24 August PDUFA date
- Additional time to enable review of newly submitted SUNFISH Part 2 data

- On track for mid 2020 EMA submission with Part 2 data fully integrated
- EU Prime designation

- Filed in China in April 2020

Risdiplam has also been filed in Brazil, Chile, Indonesia, Russia, South Korea, and Taiwan.

Anticipating submissions in many international markets in 2020 and 2021

Risdiplam: Update on clinical development program in patients with Type 1, 2 & 3 SMA

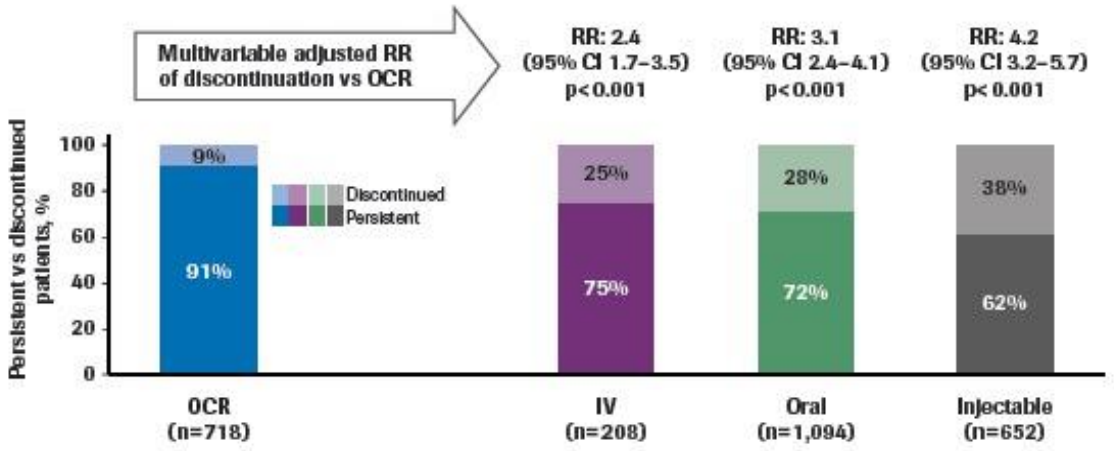
OCREVUS: Long-term disability progression and thalamic atrophy data in MS
Shorter infusion (ENSEMBLE PLUS) data and regulatory update

Paulo Fontoura, M.D. Ph.D.
Global Head Neuroscience and Rare Diseases Clinical Development

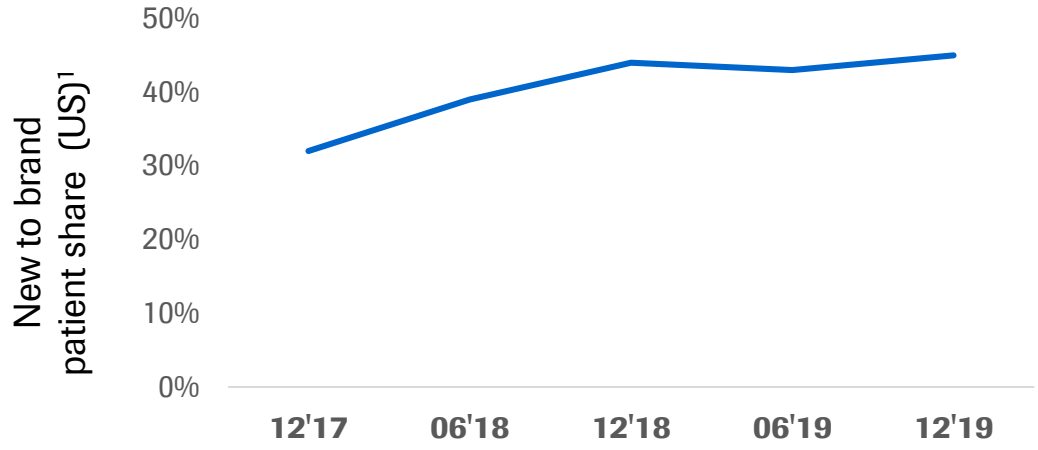
Ocrevus: first and only treatment approved for RMS and PPMS

Market leadership in US with 21% total patient share[1]

Proportion of persistant vs discontinued patients and adjusted relative risks of discontinuation by DMT group[2]



Dynamic patient share continues to grow >4/10 new patients prescribed Ocrevus in US[1]



- **Efficacy:** long-term data continue to show delay of disability progression across RMS/PPMS
- **Safety:** >150k patients treated, no unconfounded PML cases
- **Convenience:** dosing every 6 months, shorter infusion filed in EU/US
- **Access:** pricing strategy enables broad payer coverage

Source [1]Market leadership by branded product, 3 month rolling average, Symphony Health Claims Data 2019;; [2]ACTRIMS; Feb 2020
PML=Progressive multifocal leukoencephalopathy; RMS=Relapsing Multiple Sclerosis; PPMS=Primary Progressive Multiple Sclerosis; SPMS = Secondary Progressive Multiple Sclerosis; RWD = Real World Data

Ocrevus impact on key clinical and imaging markers of MS

New analysis on disability progression and loss of thalamic volume

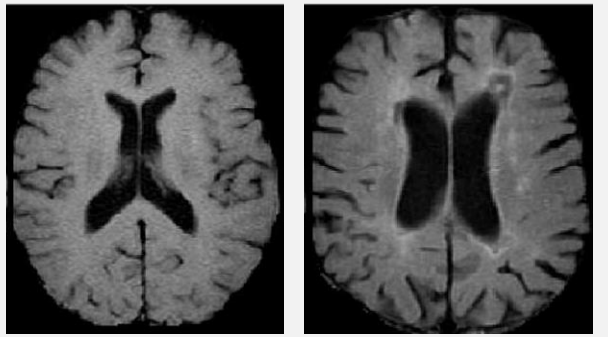
Disability progression in patients with RMS

Consequences of reaching EDSS score ≥6.0
Walking aid required

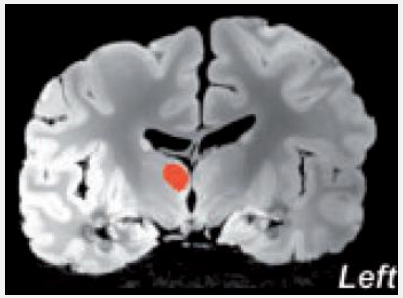
Thalamic atrophy as marker of MS-related CNS damage

Accumulation of brain atrophy in RMS[3]

Duration: 5 yrs **Duration: 10 yrs**



Thalamus is also affected[4]

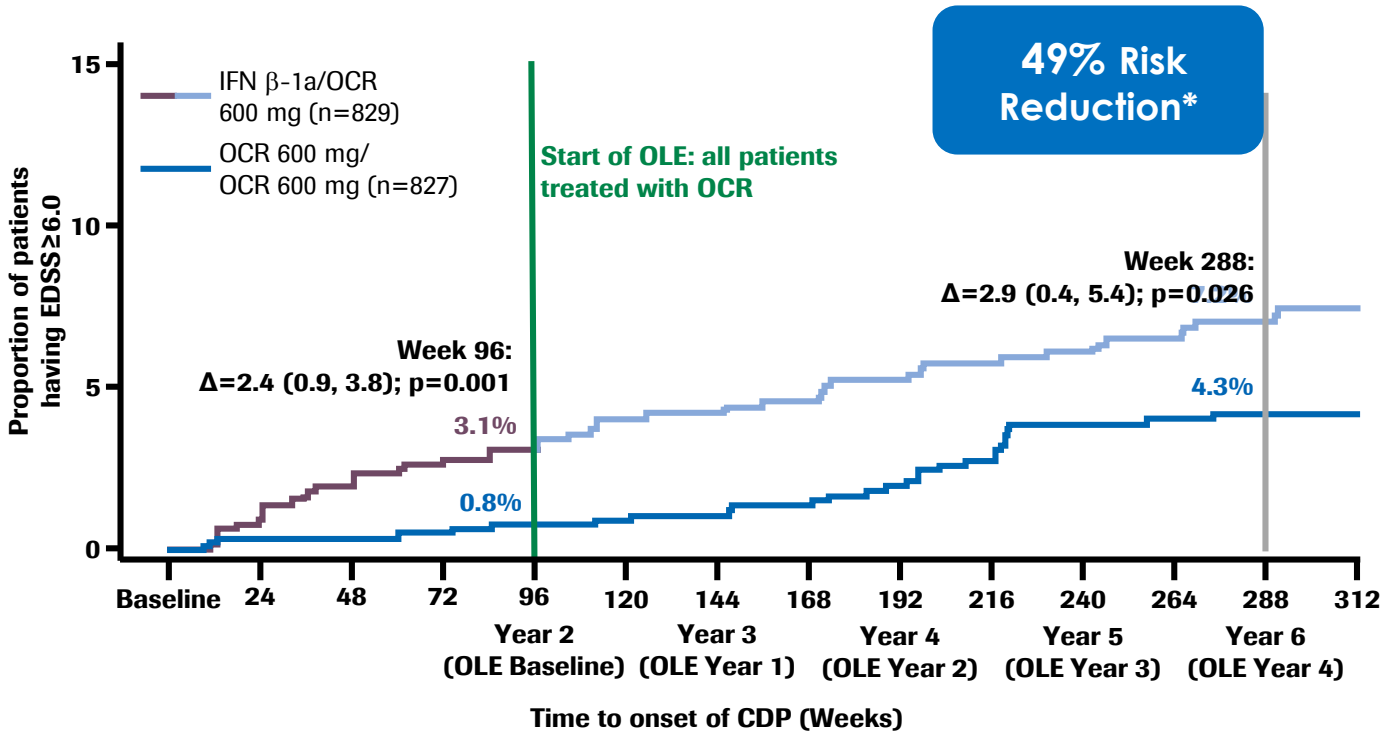


Thalamic atrophy correlates with physical and cognitive impairment

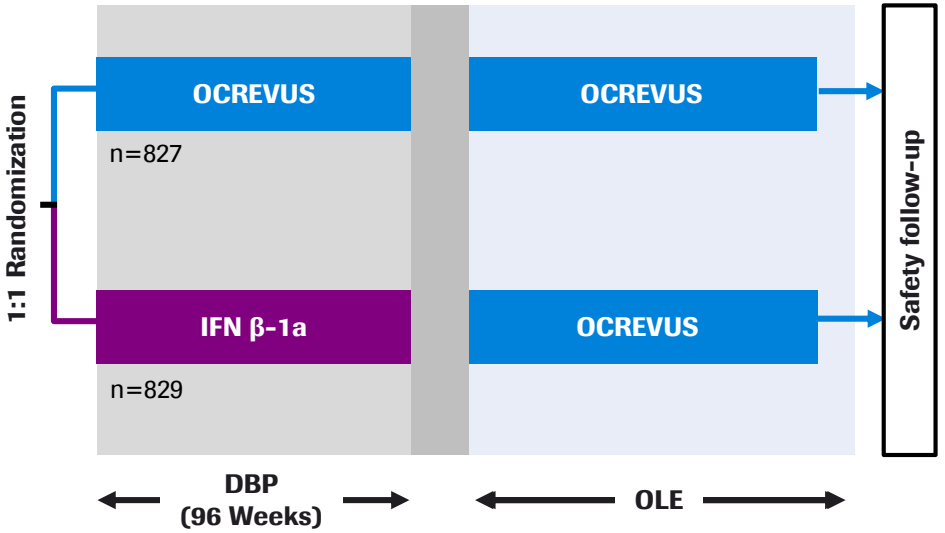
1. Tomassini V, et al. MSJ 2019;25:1306–1315. 2. Kobelt G, et al. MSJ 2017;23:1123–1136. 3.. Bermel RA, Bakshi R. Lancet Neurol 2006;5:158–70. 4. Kolasinski et al. Brain 2012: 135; 2938–2951.
EDSS=Expanded Disability Status Scale; RRMS=relapsing-remitting multiple sclerosis

Ocrevus 6 year follow up from Phase 3 OPERA studies in RMS

RMS – time to onset of EDSS≥ 6 for at least 48 weeks during DBP and OLE periods



Phase 3 OPERA study design



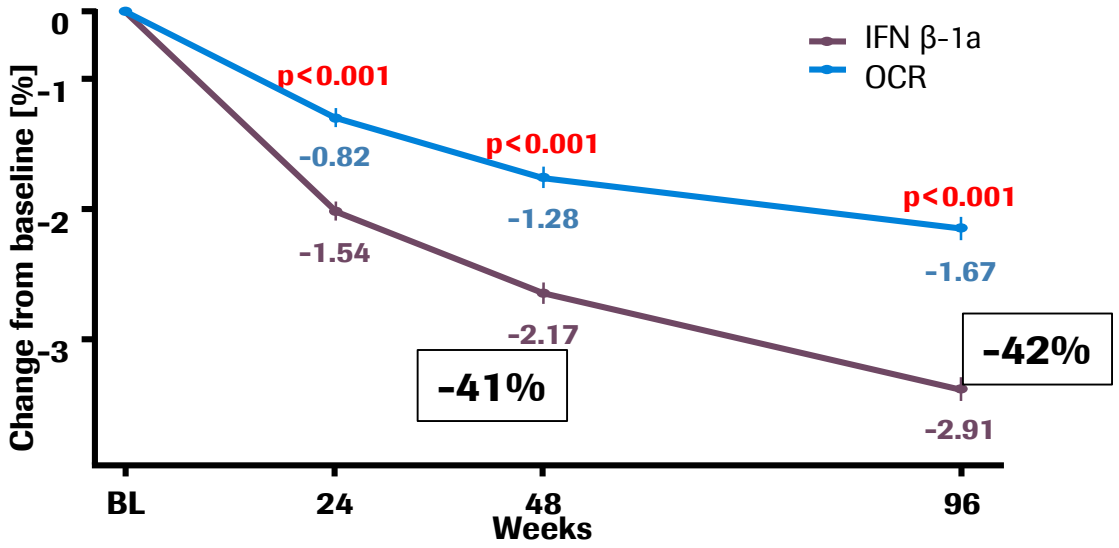
- **Ocrevus treatment reduced the risk of needing a walking aid (EDSS≥6) by 49% in RMS patients compared with patients who switched from interferon beta-1α two years later**

*The risk was measured by the length of time until a person reached a score on the Expanded Disability Status Scale six or greater (EDSS≥6) that was sustained for at least 48 weeks. (HR [95% CI]: 0.51 [0.32–0.82]; p= 0.0042)

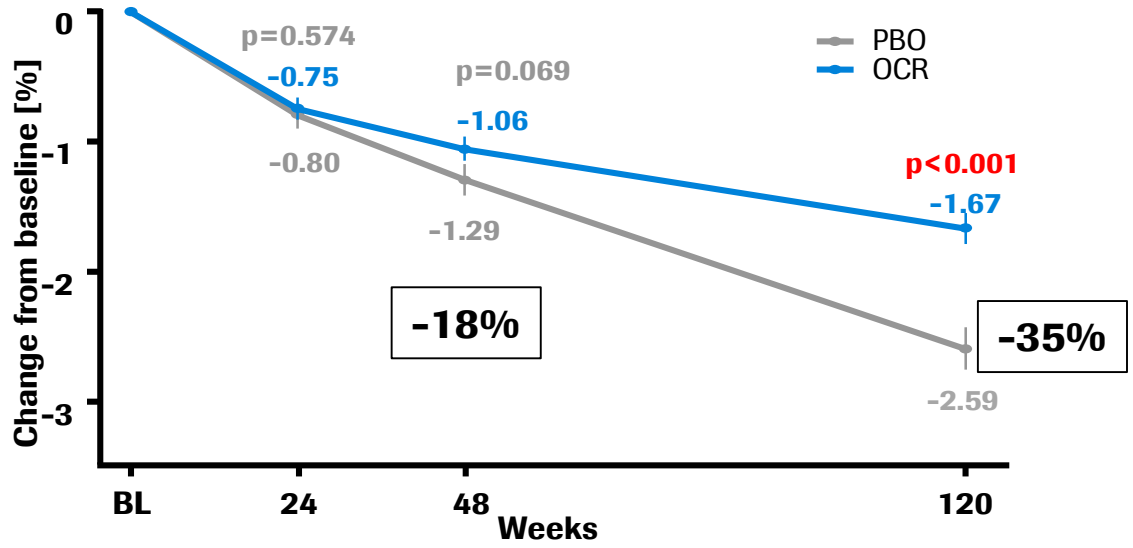
Ocrevus effect on thalamic atrophy in patients with RMS and PPMS

*Post-hoc analysis OPERA I/II & ORATORIO studies**

Change in thalamic volume Ocrevus vs IFNβ-1a in RMS (OPERA)



Change in thalamic volume Ocrevus vs pbo in PPMS (ORATORIO)

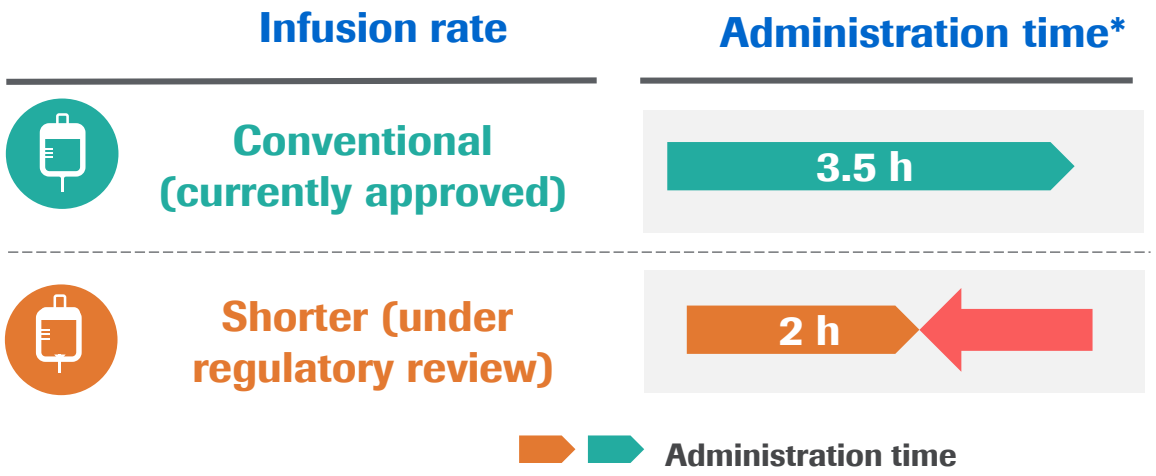


- **Ocrevus reduces loss of thalamic volume over time in both RMS and PPMS**
- **Thalamic atrophy may be a more sensitive measure of therapeutic efficacy of CNS damage**

* Thalamic atrophy (measured by change in thalamic volume); results from the double-blind periods of the Phase III OPERA I, OPERA II and ORATORIO studies
Model: Change from baseline [%] = baseline volume + geographical region (US vs. ROW) + baseline EDSS category (<4, ≥4) + week + treatment + treatment*week+ baseline volume*week + age + study (only for OPERA I/II).
IFNβ-1a; interferon beta-1a; PBO, placebo; PPMS, primary progressive multiple sclerosis; RMS, relapsing multiple sclerosis; CNS, central nervous system.

Ocrevus shorter infusion time nearly halves administration time

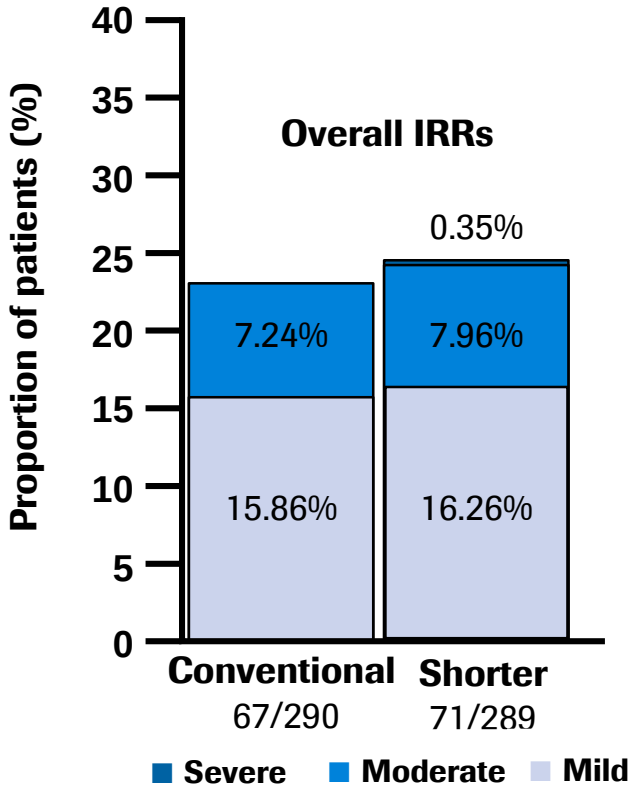
ENSEMBLE PLUS data show comparable safety



*For all six-monthly 600 mg doses after initial dose (two 300 mg intravenous (IV) infusions separated by two weeks)
Total time requires pre-medication (30min-1hr and observation 1hr)

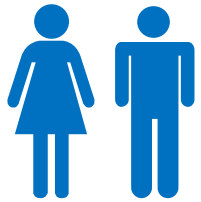
- Comparable frequency and severity of IRRs between conventional and shorter infusion periods shown, no new safety signals
- Shortening the infusion of ocrelizumab to 2 hours reduces the burden on patient and healthcare infrastructure
- Shorter infusion was filed in EU/US April 2020

IRR analysis: Primary endpoint met

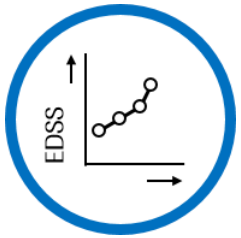


IRR - infusion-related reaction

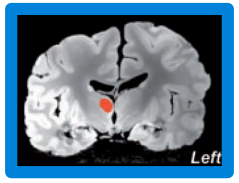
Summary



- **150,000+ people treated globally; consistent and favourable benefit-risk profile**



- **New data show clinically meaningful 49% risk reduction of disability progression**



- **OCREVUS reduces the loss of thalamic volume over time in both RMS and PPMS**

- **Shorter 2 hour infusion filed with FDA & EMA**

Doing now what patients need next