GENERATION HD2 Clinical Trial Overview (BN42489)

[Insert event/discussion title]

[Insert presenter's name]

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M-DE-00015650| *Date of preparation: February 2023*

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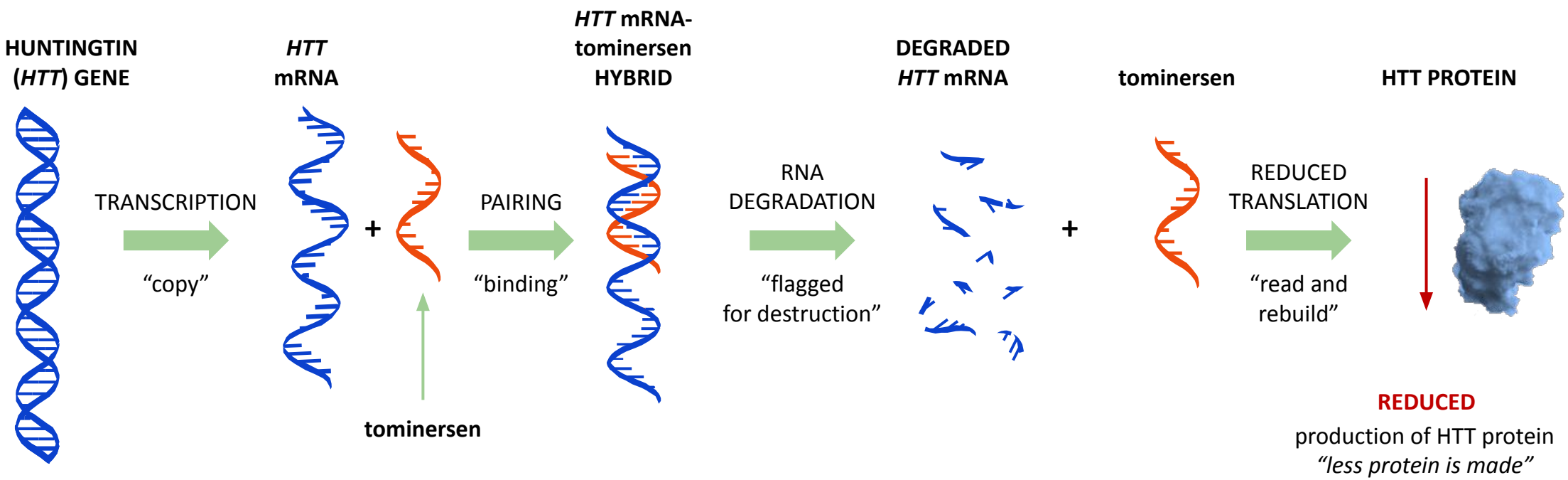
GENERATION HD 2

Tominersen is an investigational molecule designed to target the underlying genetic cause of HD



REDUCED

production of HTT protein

"less protein is made"

Abbreviations: HTT=huntingtin; mRNA=messenger riboneucleic acid.

Tominersen is an investigational (not approved) medicine that is being studied for the treatment of people with HD.

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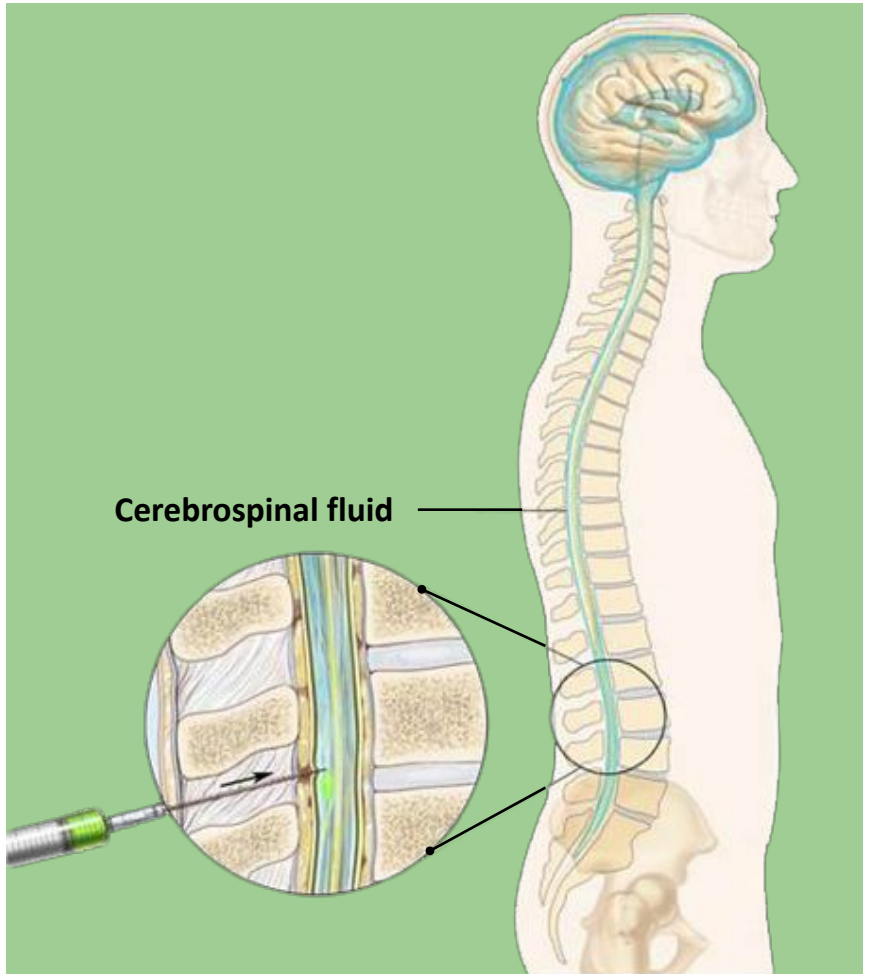
ANTISENSE DRUGS

Direct delivery to the central nervous system



Intrathecal injections

- This procedure is commonly called a lumbar puncture or ‘spinal tap’.
- The drugs injected into the lower back in the space around the spinal cord (an intrathecal injection) and travels to the brain in the cerebrospinal fluid.
- Cerebrospinal fluid is a clear fluid that surrounds the brain and spinal cord.

Image adapted from www.cancer.gov

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10-Year HD Programme History

Building on science and partnerships

2013	2015-2017	2018-2021	2022	Today/2023
Ionis/Roche HD partnership; investigational compound selected for development	Phase I/IIa study Roche licenses investigational IONIS-HTT$_{Rx}$ **(tominersen)**	Phase III programme and studies; dosing halt (GENERATION HD1 Phase III, Natural History Study, GEN-PEAK Phase I, GEN-EXTEND open-label extension)	Announcement and plans for refined tominersen focus and further HD research	Initiation of GENERATION HD2 Phase II dose-finding study

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GENERATION HD2: Testing a refined hypothesis

GENERATION HD1 exploratory *post hoc* findings

Potential benefit in younger adults with manifest HD with less disease burden and who received lower tominersen exposures

Focused population

GENERATION HD2 will focus on adults with prodromal (very early subtle symptoms) or early manifest HD (aged 25–50 years and CAP score of 400–500)

Lower and less frequent dosing

GENERATION HD2 will investigate lower and less frequent doses of tominersen

Safety, biomarkers and efficacy trends

Study evaluates safety, biomarkers and efficacy trends of two different doses of tominersen in younger adults with less disease burden

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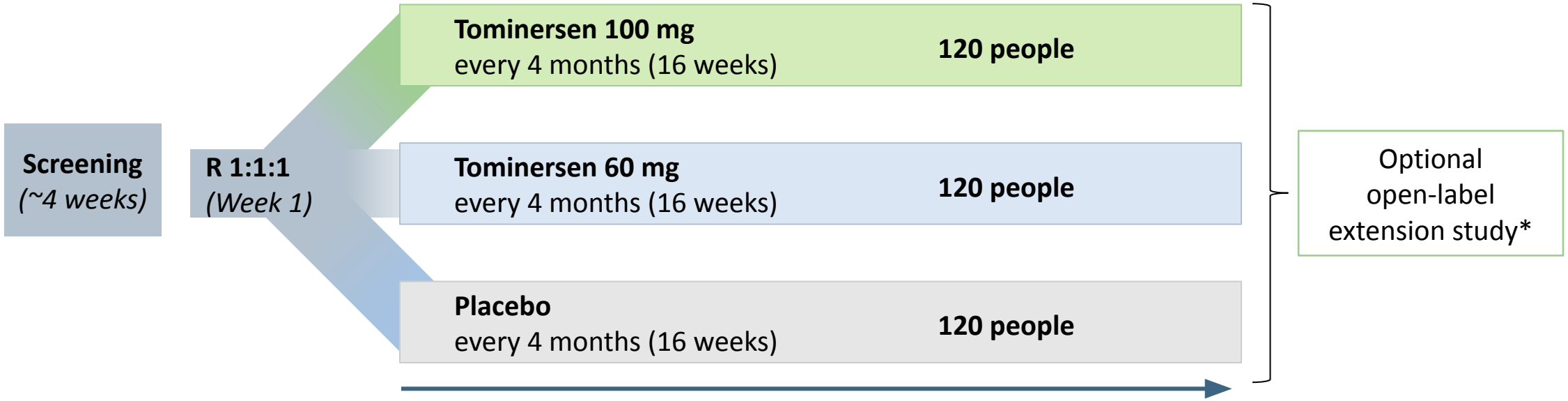
Overview of GENERATION HD2 study

A study to evaluate the safety, biomarkers and efficacy trends of **two dose levels of tominersen** in participants with **prodromal (~20/arm) and early manifest (~100/arm)** HD versus placebo



Randomised, multicenter, double-blind, placebo-controlled study
16+ months of treatment
Independent data monitoring committee reviews trial and data every 4–6 months

**Data-dependent planned study; pending approvals from clinical trial authorities.*
HD, Huntington's disease; R, randomization.
Tominersen is an investigational (not approved) medicine that is being studied for the treatment of people with HD.

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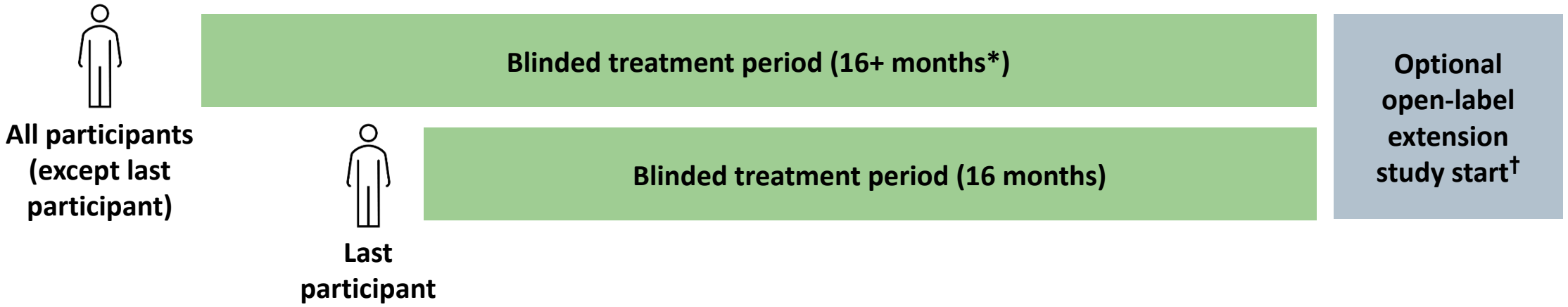
Key aspect of GENERATION HD2 study: “Common close” design



- Minimum 16-month treatment period (7 clinic visits with 4 interim phone consultations)
- The common close design means that the blinded treatment and study assessments continue for all participants until the last participant completes 16 months of treatment
- Decision about open-label extension will be data driven (e.g. appropriate dose and safety determined in study)

** Length of blinded treatment period is dependent on when the participant is randomised; † Data-dependent planned study; pending approvals from clinical trial authorities.*

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Key aspect of GENERATION HD2 study: Lower and less frequent dosing

GENERATION HD2 dosing regimen compared to the previous Phase III study

= tominersen = placebo injection = lumbar puncture only

	MONTH	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
GENERATION HD1 Previous Phase III	**120mg** Every 2 Months	●	●		●		●		●		●		●		●		●		●		●		●		●		○
	120mg Every 4 Months	●	●		○		●		○		●		○		●		○		●		○		●		○		●
	PLACEBO	○	○		○		○		○		○		○		○		○		○		○		○		○		○
GENERATION HD2 Phase II	**100mg** Every 4 Months	●				●				●	●			●				●									
	60mg Every 4 Months	●				●				●	●			●				●									
	PLACEBO	○				○				○	○			○				○									

Minimum 16-month treatment period; study continues until all participants complete 16 months of treatment

Tominersen is an investigational (not approved) medicine that is being studied for the treatment of people with Huntington's Disease.

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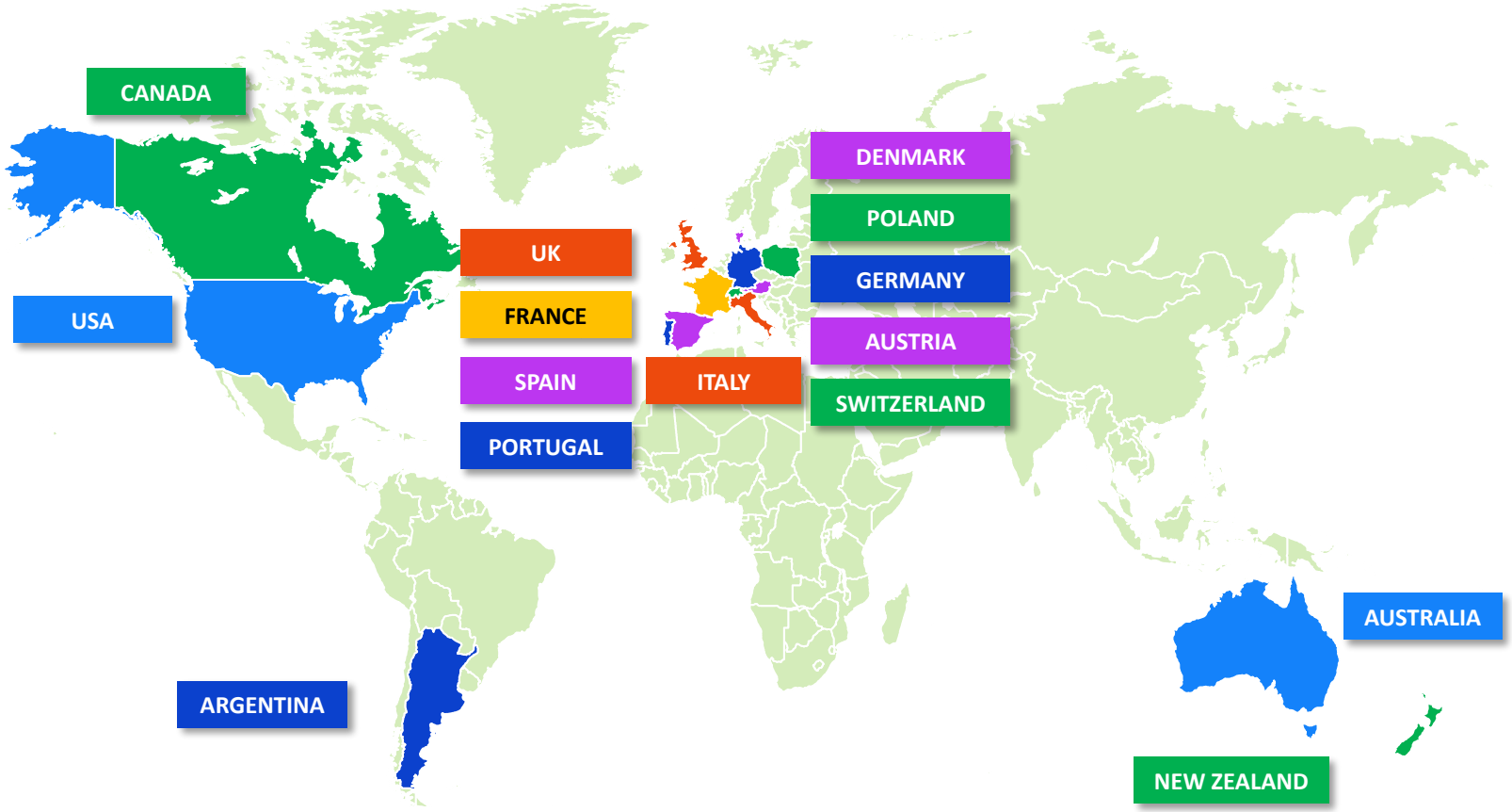
GENERATION HD2 study: Expected country participation

- Planned to run in 15 countries*
- Study is listed on clinical trial registries** and specific sites will be posted once a site is nearly ready to enroll participants; updates also available via Roche Medical Information (medinfo.roche.com)
- Interested individuals should speak to their HD specialist



** Final country participation to be confirmed. For any clinical study, it is possible that for various reasons an expected study site/country does not proceed to enrol participants. Alternatively, additional locations may be added.*
*** ClinicalTrials.gov (NCT05686551), EU Clinical Trial Registry (2022-001991-32)*

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GENERATION HD2 summary

GENERATION HD2 is a new study that will test two doses of intrathecally-administered tominersen (60 mg and 100 mg) given every 4 months

Every participant will receive tominersen or placebo for at least 16 months, and will continue until the last participant has completed the study. An iDMC will review trial data every 4–6 months

360 participants with prodromal or early manifest HD will be included, aged 25–50 years and with a CAP score of 400–500*

GENERATION HD2 is a global study expected to run in 15 countries. Interested individuals should speak to their HD specialist

** Additional inclusion and exclusion criteria apply, including the participation of a study companion*
CAP, CAG-age product; HD, Huntington's disease; iDMC, independent Data Monitoring Committee.

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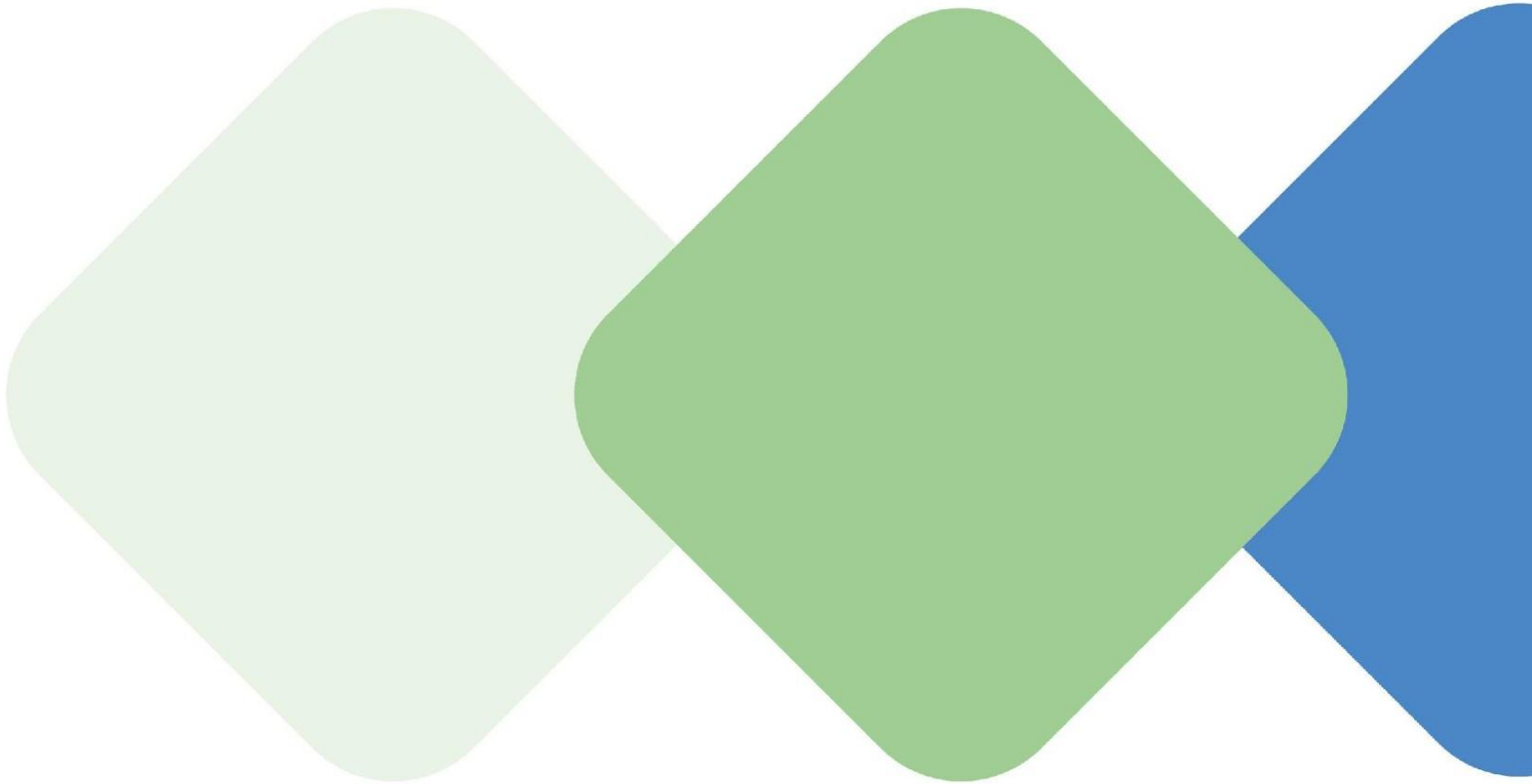
Acknowledgements and thank you

Ionis discovered tominersen and is partnered with Roche for its development
Special thanks to Frank Bennett, Holly Kordasiewicz, Eric Swayze, Roger Lane and Anne Smith

Special thanks for their collaborations

Deepest gratitude to the HD community for its ongoing contributions, especially families, investigators and site staff

Appendix



GENERATION HD2: Key inclusion/exclusion criteria

Inclusion criteria

Prodromal HD (n=~20 per arm)	Early manifest HD (n=~100 per arm)
DCL=2–3	DCL=4
IS=100	100>IS≥70 TFC ≥8
Age 25–50	
CAP 400–500	
TMS >6	
Study companion required	

Exclusion criteria

- Current or previous use of an ASO, siRNA or HTT-lowering therapy
- Anti-platelet or anticoagulant therapy
- History of gene therapy, cell transplantation, or brain surgery