Defining Pediatric Huntington Disease: Time to Abandon the Term *Juvenile Huntington Disease*?

Huntington disease (HD) is a progressive neurodegenerative disorder for which no disease-modifying treatment is available. Numerous novel approaches for treatments in HD are in development. Several clinical trials have already been conducted, and further trials are under way.[1] Onset may be at almost any age, but it is most common in mid-life. Traditionally, those with an onset age ≤20 years are said to have juvenile Huntington disease (JHD).[2] Recently, the European Medicines Agency (EMA) removed a class waiver that allowed sponsors to exclude children and adolescents from clinical studies for a number of conditions, including HD (EMA decision CW/0001/2015).[3] The EMA justified its decision as follows: "According to recent data (Roos 2011), Huntington disease may occur in the paediatric population in a juvenile form. It is reported to be about 6% of the cases of Huntington disease (which itself has a prevalence of 1/10,000) and is characterised in paediatric and adult populations by a similar molecular aberration in the HTT (huntingtin) gene."[3,4]

We would like to address problems arising from terminology because JHD more accurately means juvenile-onset HD and refers to all those who meet the criteria for the onset of signs and symptoms before the age of 21 years, the majority of whom are now adults (Fig. 1). The prevalence of those affected by HD who are still aged younger than 18 years is unknown.

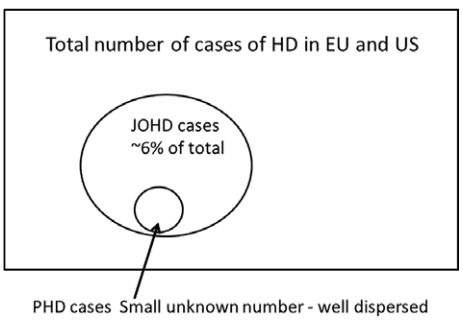

FIG. 1. The rectangle represents all the cases of Huntington disease (HD) in Europe (EU) and the United States (US). Of these, approximately 6% have an onset ≤20 years and meet the current definition of juvenile-onset HD (JOHD). Most of these cases are now adults. The number of patients meeting the definition of pediatric HD (PHD), that is, currently affected and <18 years of age, is small and unknown.

In the context of the removal of the class waiver, the use of the term *JHD* and the 6% figure is misleading. The point of removing the waiver is to force sponsors to submit a pediatric investigation plan early in the drug development process. This is meant to make them consider providing data (which could include modelling and simulation data) relevant to the pediatric cohort, although they may still apply for an individual waiver or deferral. Sponsors and regulatory agencies would benefit from a more defined terminology to refer specifically to children and young teenagers with an HD diagnosis. We propose phasing out the term *JHD* (there may be some studies that report findings prior to this change) and introducing the term *pediatric HD*. This term is simpler to understand and means young people affected by HD who are currently aged <18 years.

Although the EMA and U.S. Food and Drug Administration have similar regulations, there are subtle differences between them.[5] In the case of pediatric waivers, the statutory instruments that established the EMA and U.S. Food and Drug Administration have slightly different criteria for considering them. The U.S. Food and Drug Administration continues to include HD in the list of adult-related conditions that qualify for a waiver because they never or rarely occur in children.[6]

We agree with the EMA that those in the pediatric HD group have unmet needs, but both sponsors and regulators need to recognize that obtaining observational data following an intervention for this small, widely dispersed, cohort will be challenging.

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Neurology during the discussions on this topic and during drafting of this letter, but became an employee of F. Hoffmann La Roche, Ltd. on January 8, 2019. Roche has a drug for HD in clinical development. C.S. received honoraria for talks from: Desitin Arzneimittel GmbH, Temmler Pharma GmbH & Co. KG, AOP Pharma, and TEVA GmbH. He has provided treatment recommendations for Tetmodis (Tetrabenazine) Desitin Arzneimittel GmbH. He held a professorship (foundation) sponsored by Teva until 2010. R.A.C.R. is an advisor of UniQure. The institute received financial support for a clinical trial by TEVA. F.S. is cofounder, scientific officer, and consultant for the Italian League for Research on Huntington and related diseases (L.I.R.H. Foundation) and is a member of the JoHD/PHD advisory board for F. Hoffmann La Roche. G.B.L. is a member of the JoHD/PHD advisory board for F. Hoffmann La Roche. J.-M.B. is a member of the JoHD/PHD advisory board for F. Hoffmann La Roche.