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Repeat dosing of rocuronium 1.2 mg kg^{-1} after reversal of neuromuscular block by sugammadex 4.0 mg kg^{-1} in anaesthetized healthy volunteers: a modelling-based pilot study

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Key points

- Re-use of rocuronium within 24 h in a patient receiving sugammadex is currently not recommended.
- High-dose rocuronium given 5–60 min after sugammadex reversal produced full neuromuscular block.
- The onset time varied inversely with the time gap from sugammadex dose, and duration of action varied directly.
- Re-use of rocuronium is possible but there is considerable variability.

Background. Re-intubation and re-operation may occasionally be required after neuromuscular block (NMB) reversal. This study evaluated block onset times of a second dose of rocuronium (1.2 mg kg^{-1}) after sugammadex reversal of rocuronium 0.6 mg kg^{-1}.

Methods. In this open-label study of healthy anaesthetized volunteers, subjects received rocuronium 0.6 mg kg^{-1}, were antagonized at 1–2 post-tetanic counts with sugammadex 4.0 mg kg^{-1}, and received rocuronium 1.2 mg kg^{-1} at 5, 7.5, 10, 15, 20, 22.5, 25, 27.5, 30, 45, or 60 min after sugammadex. Spontaneous recovery occurred after repeat rocuronium dose. Primary endpoints were the onset time of maximal block (time to lowest T_1 value reached) and the clinical duration of block (until T_1=25%) after repeat rocuronium dose.

Results. Sixteen subjects were included. For subjects receiving rocuronium 1.2 mg kg^{-1} 5 min after sugammadex (n=6), mean (SD) onset time (to T_1=0) was 3.06 (0.97) min; range, 1.92–4.72 min. For repeat dose time points ≥25 min (n=5), mean onset was faster (1.73 min) than for repeat doses <25 min (3.09 min) after sugammadex. The duration of block ranged from 17.7 min (rocuronium 5 min after sugammadex) to 46 min (repeat dose at 45 min). Mean duration was 24.8 min for repeat dosing <25 min *vs* 38.2 min for repeat doses ≥25 min.

Conclusions. Rapid re-onset of NMB occurred after repeat dose of rocuronium 1.2 mg kg^{-1} as early as 5 min after sugammadex in healthy volunteers. Re-onset of block took longer if second rocuronium dose was <25 min after sugammadex. The duration of action of second rocuronium dose increased with later repeat dose time points.

Keywords: neuromuscular block; repeat dose; reversal; rocuronium; sugammadex

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Sugammadex, a modified γ-cyclodextrin, is designed to specifically bind with the steroidal neuromuscular blocking agents rocuronium and vecuronium with high affinity.[1] Phase I–III trials have shown that sugammadex safely and effectively antagonizes both moderate and deep rocuronium-induced neuromuscular block (NMB).[2–9]

In clinical practice, patients may occasionally require re-operation in the immediate postoperative period, soon after successful reversal of rocuronium-induced NMB by sugammadex, and re-establishment of block is likely to be required. One of the options in such situations would be to re-administer rocuronium. It is currently recommended that after initial reversal of NMB with sugammadex, 24 h should be allowed before rocuronium can be re-administered.[10] This conservative recommended waiting time is based on the maximum clearance time for sugammadex in all patients. Consequently, it is recommended that in the case of need for NMB before this time interval, succinylcholine or a benzylisoquinoline neuromuscular blocking agent should be given. However, the required dosage for succinylcholine or a benzylisoquinoline neuromuscular blocking agent is uncertain, as it is currently unknown whether the pharmacodynamic profile of depolarizing or non-depolarizing neuromuscular blocking agents is adversely affected after reversal of rocuronium by sugammadex.

Rocuronium is associated with minimal cardiovascular effects in doses up to the highest recommended of

1.2 mg kg^{-1}.[11 12] It can be calculated that after sugammadex 4.0 mg kg^{-1}, which is the dose often used in clinical practice, a repeat dose of ~1.2 mg kg^{-1} would be sufficient to bind the remaining free sugammadex.[13] This is based on sugammadex and rocuronium forming a complex in a 1:1 molar ratio, which, considering their respective molecular weights, corresponds to a 3.3:1 mg kg^{-1} sugammadex: rocuronium ratio.[14] As the currently recommended waiting time of 24 h for repeat administration of rocuronium after sugammadex reversal of NMB is based on conservative pharmacokinetic considerations, in clinical practice, earlier administration of a repeat dose of rocuronium may be acceptable. This study was designed to evaluate the onset times of NMB at variable times of repeat dose of 1.2 mg kg^{-1} rocuronium after reversal of NMB by 4.0 mg kg^{-1} sugammadex in anaesthetized healthy volunteers. The 4.0 mg kg^{-1} dose was selected as this is the recommended dose for reversal of deep [1–2 post-tetanic counts (PTCs)] NMB. Moreover, this study aimed to provide more accurate guidance with regards to the safe timing of a repeat dose of 1.2 mg kg^{-1} rocuronium in the case of the need for re-operation and NMB after reversal with sugammadex.

Methods

This was a single-centre, open-label study in healthy volunteers, with variable times of repeat dose of rocuronium after NMB reversal by sugammadex. Subjects were dosed one at a time. The study was approved by the Independent Ethics Committee of the trial centre and was conducted in compliance with the current revision of the Declaration of Helsinki, International Conference on Harmonization guidelines and Good Clinical Practice, and current regulatory requirements.

Healthy male and female volunteer subjects aged 18–45 yr, with a BMI of 18–30 kg m^{-2}, normal arterial pressure (AP) (systolic/diastolic $<$140/$<$90 mm Hg), and heart rate ($>$45 to $<$90 beats min^{-1}) and in good, age-appropriate, healthy condition, were enrolled in the study. Subjects were excluded if they had a Mallampati score of III or IV or a history of difficult intubation; and had a family history of malignant hyperthermia, or positive hepatitis B or C, or human immunodeficiency virus serology results at screening. Subjects were excluded if they were taking medication of any kind 2 weeks before study commencement other than acetaminophen, non-steroidal anti-inflammatory drugs, and oral contraceptives. Subjects with a history of drug, solvent, or alcohol abuse, and those smoking $>$15 cigarettes/day, were also excluded. All subjects were required to give written informed consent before enrolment in the study.

It was planned to use distinct time points for the repeat dose of rocuronium to evaluate the relationship between time point of repeat dose after sugammadex reversal and onset time and duration of NMB. The time point of the repeat dose of rocuronium for the next subject was determined by an online safety evaluation held after each subject. The next time point for the repeat dose was based upon the TOF-Watch® results, safety/tolerability information, and the recommendation of the investigator. Where possible, the results of non-linear regression modelling were also taken into account in this decision. The optimal next time point of repeat dose was estimated based on previous onset times and durations of NMB measured for all previous subjects, and used the following model:

$$E[\text{time of onset (time of re-use)}] = F(\text{time of re-use}, \alpha),$$

where F is a (non-)linear mathematical function of the repeat dose time and α a vector of the set of parameters of the model to be estimated. The link function F was chosen such that either a sigmoid curve or an exponentially decreasing curve would be used, depending on which model better fitted the data.

On the basis of calculations using molar amounts of both drugs and elimination half-life considerations, the recommended safe starting time for the repeat dose of rocuronium was selected to be 1 h after administration of sugammadex for the first subject and was not to exceed 5 h for the next subjects.

Anaesthesia was induced using a propofol i.v. blood target controlled infusion, with propofol 2–4 μg ml^{-1} titrated until loss of eyelash reflex, and remifentanil 0.1–0.3 μg kg^{-1} min^{-1}. Subjects were preoxygenated with 100% oxygen for 5 min before placement of a laryngeal mask airway and ventilation to normocapnia with an air–oxygen mixture. Rocuronium 0.6 mg kg^{-1} was given as an i.v. bolus dose, and at a PTC of 1–2, reversal was with sugammadex 4.0 mg kg^{-1}. At various time points after sugammadex, rocuronium 1.2 mg kg^{-1} was administered. Sedation, ventilation, and neuromuscular monitoring continued until (spontaneous) recovery from repeat NMB (T_4/T_1 ratio $\geq$0.9 for at least 10 min) and stopped when considered safe by the anaesthetist. Anaesthesia was maintained throughout the study where rocuronium was used first and then given as a repeat dose.

Neuromuscular function was monitored by acceleromyography, using the TOF-Watch® SX (Organon Ireland Ltd, a division of MSD, Swords, Co. Dublin, Ireland) at the adductor pollicis muscle. Monitoring started after the induction of anaesthesia (before rocuronium administration) and continued until at least 10 min after recovery of the train-of-four (TOF) ratio to 0.9. Repetitive TOF stimulation was applied every 15 s at the ulnar nerve. Neuromuscular data were collected via a transducer fixed to the thumb and the TOF-Watch® SX monitoring program. TOF-Watch® SX calibration was performed $>$3 min after a 5 s, 50 Hz tetanic stimulation and was preceded by a 1 min repetitive TOF stimulation. Peripheral body temperature was measured continuously by a thermistor at the thenar eminence of the palm and maintained at $\geq$32°C. After rocuronium administration and the T_1 response had disappeared, PTC stimulation was started with a 5 s, 50 Hz tetanic stimulation every 2 min. After a 3 s pause, stimulations were performed at a frequency of 1 Hz for 15 s. Spontaneous recovery was allowed to progress until the appearance of 1–2 PTCs when sugammadex

4.0 mg kg^{-1} was administered. In order to assure T_1 was at 100% before repeat dosing of rocuronium, a mandatory calibration/setup adjustment was introduced just before the repeat dose of rocuronium. After the second dose of rocuronium, TOF stimulation continued every 15 s until at least 10 min after recovery of the TOF ratio to 0.9. For all T_1 determinations, a T_1 normalization procedure was performed.[15]

Adverse events (AEs) and serious AEs (SAEs) were recorded and coded using the Medical Dictionary for Regulational Activities (version 11.1). Oxygen saturation was monitored by pulse oximetry, until ≥8 h after discontinuing anaesthesia, and vital signs (heart rate and AP) were measured at screening, during anaesthesia, and at follow-up. Tympanic body temperature was measured before anaesthesia and every 30 min during anaesthesia.

Subjects were evaluated for signs of residual block or re-occurrence of block, which was measured as a decline in the T_4/T_1 ratio to ≤0.8 in at least three consecutive TOF values after administration of sugammadex and before the repeat dose of rocuronium. If spontaneous recovery was judged as unacceptably long (>120 min) after the repeat rocuronium dose, a dose of 2.0 mg kg^{-1} sugammadex could be given at the first signs of recovery.

The sample size and power calculations were based on simulations, assuming an exponential decrease in the onset time of NMB to a minimum value with late repeat dose times. It was expected that a minimum of 10 and a maximum of 20 subjects would be treated. The strength of the relationship between onset time of block after rocuronium repeat dose and time of repeat dose after sugammadex administration was important in the decision to proceed beyond 10 subjects. The shortest acceptable time point of rocuronium repeat dose was determined as the first time point of repeat dose after sugammadex administration for which the one-sided upper 95% confidence limit for the onset time of block was <4 min. A sample size of 20 subjects, with rocuronium repeat dose at variable time points up to six half-lives of the assumed exponentially decreasing curve of onset time with increasing repeat dose time, was calculated to provide a power >85% to derive from the non-linear model fit a repeat dose time which gives 95% confidence in an onset time of block <4 min.

During the study online safety evaluations, rapid onset of NMB was observed when rocuronium was repeated only 5 min after sugammadex, and it was thus decided to estimate the onset time of block after rocuronium repeat dose at 5 min more accurately. Therefore, under the conservative assumption of a geometric mean onset time of 4 min and a SD of 0.3 of the log-values of onset times, six volunteers with repeat dose of rocuronium at 5 min after sugammadex were considered sufficient to obtain an upper limit of the two-sided 95% confidence limit below 5.5 min (i.e. <1.5 min above the geometric mean onset time to block).

The primary objectives were to determine the onset time of NMB after rocuronium repeat dose, which was assessed as the time from the start of repeat dose of rocuronium to maximum block (lowest T_1 value achieved) and the clinical duration of NMB after rocuronium repeat dose, which was assessed as the time from the start of the repeat dose of rocuronium to recovery of T_1=25%. Both the time to onset of NMB and the duration of block after repeat rocuronium dose were modelled against the time of repeat dose using either a sigmoid or exponential model. The final model choice was selected based on a comparison of model fits of each of these models, applying the model constraint that for late time points of repeat use of rocuronium, the model had to approach an asymptotic value of the known and reported onset times and durations of NMB as achieved after an initial dose of rocuronium 1.2 mg kg^{-1}. Modelling was performed using NONMEM VI and corresponding plots generated using Splus 6.2.1 under Windows XP operating system. Goodness of fit was judged based on model fits, goodness-of-fit plots, residual plots, and standard errors of the estimated model parameters.

The relationship between the time to onset of NMB and the time of repeat dose of rocuronium after sugammadex administration was best described by a sigmoid model:

$$T_{on}(t) = T_{max} - (T_{max} - T_{min}) \times t^{\gamma} / (t^{\gamma} + T_{50}^{\gamma})$$

where $T_{on}(t)$ is the onset time after rocuronium repeat dose at time t after sugammadex, T_{max} the maximum onset time, T_{min} the minimum onset time T_{50} the time point of repeat dose at which an onset time of $(T_{max}+T_{min})/2$ is reached, and γ the sigmoidicity factor (Hill's coefficient).

The dependence between the duration of NMB and the time of repeat dose of rocuronium after sugammadex administration was again evaluated by a sigmoid model:

$$T_{dur}(t) = T_{min} + (T_{max} - T_{min}) \times t^{\gamma} / (t^{\gamma} + T_{50}^{\gamma})$$

where T_{dur} (t) is the duration of NMB after rocuronium repeat dose at time t after sugammadex, T_{max} the maximum duration (fixed to 67 min), T_{min} the minimum duration, T_{50} the time point of repeat dose at which a duration of $(T_{max}+T_{min})/2$ is reached, and γ the sigmoidicity factor (Hill's coefficient).

Results

This study was conducted at a single site between April and September 2008. A total of 17 subjects were enrolled in this study. One subject received neither sugammadex nor the repeat dose of rocuronium because incomplete NMB or direct stimulation during neuromuscular transmission monitoring was encountered after administration of the first rocuronium dose. In this subject, no sugammadex had been administered and anaesthesia was discontinued as soon as the TOF spontaneously increased to >0.9 for 10 min. With the exception of this subject, all subjects completed the trial according to the protocol, and there were no premature discontinuations from the study (Table 1).

The mean (SD) time from the start of first use of rocuronium 0.6 mg kg^{-1} to complete NMB (T_1=0%) was 1.25 (0.21) min, with a range of 0.95–1.57 min (n=16). After sugammadex reversal, the repeat dose of rocuronium

1.2 mg kg^{-1} produced rapid onset with complete block (T_1=0%). At the shortest rocuronium repeat dose time tested of 5 min after sugammadex reversal (n=6), mean (SD) onset of NMB was 3.06 (0.97) min (median: 2.74, range 1.92–4.72 min) (Table 2). With rocuronium repeat dose times ≥25 min (n=5), NMB onset was faster compared with earlier repeat dose times (Table 2). Mean onset time was 3.09 min for repeat dosing <25 min after sugammadex and 1.73 min for repeat doses ≥25 min.

The fitted sigmoid model shows that if a repeat dose of rocuronium 1.2 mg kg^{-1} is initiated >30 min after sugammadex 4.0 mg kg^{-1} reversal, NMB onset times are <2 min with 95% confidence (Fig. 1). For a repeat dose of 1.2 mg kg^{-1} rocuronium <25 min after reversal with sugammadex, onset times are <4.25 min with 95% confidence.

Clinical duration of NMB (until T_1=25%) was longer for the later rocuronium repeat dose times, ranging from 17.7 min (5 min after sugammadex) to 46 min (repeat dose at 45 min) (Table 2). In subjects with a rocuronium repeat dose time of 5 min, the mean duration of block was 25.3 min (range 17.7–41.0 min) (Table 2). Mean duration of block was 24.8 min for repeat dosing <25 min and 38.2 min for repeat doses ≥25 min after sugammadex. One subject (with a second dose of rocuronium 5 min after sugammadex) received a second dose of sugammadex (2.0 mg kg^{-1}) because recovery time exceeded 2 h and fully recovered from NMB within a few minutes.

The fitted sigmoid model and two-sided 90% confidence limit (5th and 95th percentiles) (Fig. 2) show that with a rocuronium repeat dose at 25 min, a block duration of ~30 min was predicted with a one-sided lower 95% confidence limit of ~20 min.

Overall, seven subjects experienced at least one AE of mild-to-moderate intensity. Headache (n=4) was the only AE reported by more than one subject. Only one SAE occurred. The subject, a 24-yr-old female, had normal study assessments performed at screening and during the day of administration of trial medication and she was in a good physical and mental condition. The subject received the second dose of rocuronium 5 min after sugammadex administration, and, because her recovery time exceeded 2 h, a second dose of sugammadex (2.0 mg kg^{-1}) was administered. During the first hour after waking-up from anaesthesia, the subject felt anxious and displayed psychotic behaviour, which lasted ~1 h and was considered to be of moderate intensity and possibly related to the study drug. The subject recovered within 1 h without further treatment and completed the study according to the protocol. During additional questioning, this subject admitted that she had previously experienced a psychotic episode lasting for a month, 5 yr before the start of the study.

Table 1 Physical characteristics for all subjects receiving a repeat dose of rocuronium (n=16). BMI, body mass index

Sex [n (%)]	
Male	8 (50)
Female	8 (50)
Age (yr) (range)	19–41
Weight (kg) (range)	52.7–96.5
Height (cm) (range)	161–190
BMI (kg m^{-2}) (range)	18.9–28.0

Table 2 Individual onset times (T_1=0%) of NMB relative to rocuronium repeat dose and NMB duration, n=16. *Subject received a second i.v. dose of sugammadex (2 mg kg^{-1}) because recovery time after repeat dose of rocuronium exceeded 2 h

Rocuronium repeat dose time point relative to start of sugammadex administration (min)	Neuromuscular block onset time (T_1=0%) relative to start of first use of rocuronium (min)	Neuromuscular block onset time (T_1=0%) relative to start of rocuronium repeat dose (min)	Clinical duration of rocuronium repeat dose neuromuscular block (T_1=25% recovery) (min)	Time to recovery of train-of-four ratio to 0.9 after rocuronium repeat dose (min)
5.0	1.50	4.72	30.0	68.8
5.0*	1.18	2.75	41.0	120.0
5.0	0.98	1.92	22.4	58.3
5.0	1.12	2.68	17.7	34.3
5.0	1.17	2.73	22.7	43.0
5.0	1.57	3.57	17.8	47.5
7.5	1.10	2.35	24.6	46.8
10.0	0.95	3.48	19.7	42.5
15.0	1.48	2.80	26.6	41.0
20.0	1.40	3.15	21.4	36.3
22.5	1.42	3.83	29.1	52.5
25.0	1.30	2.05	37.3	82.3
27.5	1.52	2.60	34.4	71.3
30.0	0.97	1.43	29.9	59.0
45.0	1.23	1.23	46.0	94.5
60.0	1.10	1.32	43.6	70.5

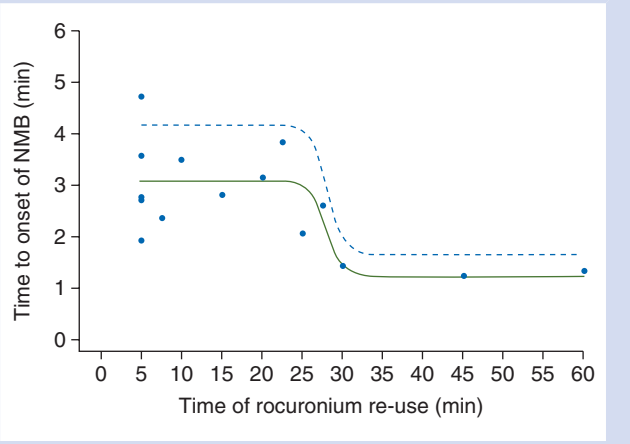

Fig 1 Relationship between the mean time to onset of NMB and the time of rocuronium repeat dose. Green line, predicted model; blue dotted line, one-sided upper 95% confidence limit (95th percentile).

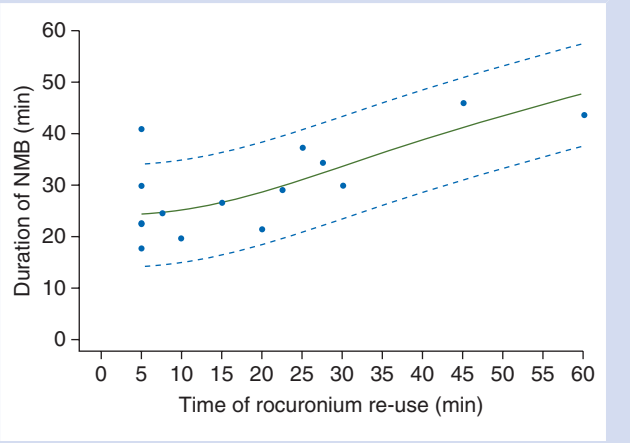

Fig 2 Relationship between the clinical duration of NMB and the time of rocuronium repeat dose. Green line, predicted model; blue dotted lines, two-sided 90% confidence limit (5th and 95th percentiles).

Discussion

This study evaluated whether a repeat dose of rocuronium can be used in the case of the need for re-operation and re-establishment of NMB after reversal with sugammadex. There was an inverse relationship between the onset time and the time interval between sugammadex and the repeat dose of rocuronium, and a direct relationship between the duration of NMB and the time interval between sugammadex and the repeat dose of rocuronium. There was a rapid re-onset of NMB after repeat dose of rocuronium 1.2 mg kg^{-1} as early as 5 min after sugammadex.

Non-linear model results showed that if a repeat dose of rocuronium 1.2 mg kg^{-1} is initiated >30 min after sugammadex 4.0 mg kg^{-1} reversal, NMB onset times are achieved in <2 min with 95% confidence, and onset times are, with 95% confidence, below 4.25 min if given <25 min after reversal of sugammadex. It is unclear why there is a sudden decrease in the time to onset of the second block between 25 and 30 min. However, an important model constraint for the time to onset of second block was that for longer repeat dose times of rocuronium, the model had to approach the asymptotic value of the known and reported onset times achieved after initial dose of rocuronium 1.2 mg kg^{-1}. At the later times, the second dose of rocuronium will behave similarly to a first dose of 1.2 mg kg^{-1}, as the initial dose of rocuronium and sugammadex will no longer be active. With the sigmoid model, this asymptotic value is obtained. However, based on the limited number of data points, no firm conclusion can be drawn as to whether there is a sudden or more gradual decrease.

The relatively rapid onset time of NMB after only a 5 min interval may be explained by the ratio of molar concentrations of free sugammadex and rocuronium. After the repeat dose, the subjects reverted to the previous level of block (i.e. a PTC of 1–2) as the molar concentration of rocuronium administered at repeat dose corresponded to the previously administered molar concentration of sugammadex.

A plausible explanation for the shorter duration of NMB at shorter repeat dose times is that early after sugammadex reversal, a considerable amount of sugammadex remains available to reverse the second dose of rocuronium. However, with time, less sugammadex is available. The increasing duration of action of high-dose rocuronium after sugammadex reversal (Fig. 2) shows that even at the 60 min interval, NMB duration did not reach a plateau and may have further increased with time. However, along with the inter-individual variability observed with repeat rocuronium administration,[16] re-administration of high-dose rocuronium after sugammadex reversal makes the resultant duration of NMB unpredictable. This may support the argument that succinylcholine or benzylisoquinoline, depending on the clinical scenario, would be a more reasonable approach to NMB after sugammadex reversal. The variability in onset time and duration of block may also limit the confidence with which time intervals for the use of a second dose of rocuronium after sugammadex could be recommended.

In conclusion, after reversal of rocuronium-induced NMB with sugammadex, NMB can again be induced with rocuronium, and the time-course of action is related to the time interval between sugammadex reversal and repeat dose of rocuronium. Complete block was achieved when rocuronium 1.2 mg kg^{-1} was given 5 min after sugammadex administration and was associated with a mean NMB duration of 25.3 min.

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well as opinions on analysis, conclusions, and interpretation of the study data, were the responsibility of the authors.

Conflict of interest

G.C. has over the years received research grants as well as lecture fees from MSD and performed funded research on sugammadex (phase I and II studies). M.H., P.G., and P.P. are employees of MSD, Oss, The Netherlands. P.-J.K. is a consultant of MSD, Oss, The Netherlands.

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