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ORIGINAL ARTICLE ***Infertility***

Gonadotrophins or clomiphene citrate in women with normogonadotropic anovulation and CC failure: does the endometrium matter?

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STUDY QUESTION: Is endometrial thickness (EMT) a biomarker to select between women who should switch to gonadotropins and those who could continue clomiphene citrate (CC) after six failed ovulatory cycles?

SUMMARY ANSWER: Using a cut-off of 7 mm for EMT, we can distinguish between women who are better off switching to gonadotropins and those who could continue CC after six earlier failed ovulatory CC cycles.

WHAT IS ALREADY KNOWN: For women with normogonadotropic anovulation, CC has been a long-standing first-line treatment in conjunction with intercourse or intrauterine insemination (IUI). We recently showed that a switch to gonadotropins increases the chance of live birth by 11% in these women over continued treatment with CC after six failed ovulatory cycles, at a cost of €15 258 per additional live birth. It is unclear whether EMT can be used to identify women who can continue on CC with similar live birth rates without the extra costs of gonadotropins.

STUDY DESIGN, SIZE, DURATION: Between 8 December 2008 and 16 December 2015, 666 women with CC failure were randomly assigned to receive an additional six cycles with a change to gonadotropins ($n = 331$) or an additional six cycles continuing with CC ($n = 335$), both in conjunction with intercourse or IUI. The primary outcome was conception leading to live birth within 8 months after randomisation. EMT was measured mid-cycle before randomisation during their sixth ovulatory CC cycle. The EMT was available in 380 women, of whom 190 were allocated to gonadotropins and 190 were allocated to CC.

PARTICIPANTS/MATERIALS, SETTING, METHODS: EMT was determined in the sixth CC cycle prior to randomisation. We tested for interaction of EMT with the treatment effect using logistic regression. We performed a spline analysis to evaluate the association of EMT with chance to pregnancy leading to a live birth in the next cycles and to determine the best cut-off point. On the basis of the resulting cut-off point, we calculated the relative risk and 95% CI of live birth for gonadotropins versus CC at EMT values below and above this cut-off point. Finally, we calculated incremental cost-effectiveness ratios (ICER).

MAIN RESULTS AND THE ROLE OF CHANCE: Mid-cycle EMT in the sixth cycle interacted with treatment effect ($P < 0.01$). Spline analyses showed a cut-off point of 7 mm. There were 162 women (45%) who had an EMT ≤ 7 mm in the sixth ovulatory cycle and 218 women

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(55%) who had an EMT > 7 mm. Among the women with EMT ≤ 7 mm, gonadotropins resulted in a live birth in 44 of 79 women (56%), while CC resulted in a live birth in 28 of 83 women (34%) (RR 1.57, 95% CI 1.13–2.19). Per additional live birth with gonadotropins, the ICER was €9709 (95% CI: €5117 to €25 302). Among the women with EMT > 7 mm, gonadotropins resulted in a live birth in 53 of 111 women (48%) while CC resulted in a live birth in 52 of 107 women (49%) (RR 0.98, 95% CI 0.75–1.29).

LIMITATIONS, REASONS FOR CAUTION: This was a post hoc analysis of a randomised controlled trial (RCT) and therefore mid-cycle EMT measurements before randomisation during their sixth ovulatory CC cycle were not available for all included women.

WIDER IMPLICATIONS OF THE FINDINGS: In women with six failed ovulatory cycles on CC and an EMT ≤ 7 mm in the sixth cycle, we advise switching to gonadotropins, since it improves live birth rate over continuing treatment with CC at an extra cost of €9709 to achieve one additional live birth. If the EMT > 7 mm, we advise to continue treatment with CC, since live birth rates are similar to those with gonadotropins, without the extra costs.

STUDY FUNDING/COMPETING INTEREST(S): The original MOVIN trial received funding from the Dutch Organization for Health Research and Development (ZonMw number: 80-82310-97-12067). C.B.L.A. reports unrestricted grant support from Merck and Ferring. B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy for Merck, ObsEva, IGENOMIX and Guerbet. All other authors have nothing to declare.

TRIAL REGISTRATION NUMBER: Netherlands Trial Register, number NTR1449

Key words: PCOS / ovulation induction / gonadotropins / clomiphene citrate / endometrial thickness

Introduction

Normogonadotropic anovulation WHO type II is one of the most common conditions in reproductive aged women with a prevalence of 8–13% (Balen *et al*., 2016; Teede *et al*., 2018; Costello *et al*., 2019a). Clomiphene citrate (CC) has long been used as first-line treatment for ovulation induction in these women. Although ovulation is restored in about 75% of women starting ovulation induction with CC, six cycles of treatment leads to conception in only about half of these women. Women who ovulate on CC but have not conceived after six ovulatory cycles of intercourse or intrauterine insemination (IUI) are traditionally defined as having CC failure. For these women, gonadotropins are second-line pharmacological agents (moderate quality of evidence) (Teede *et al*., 2018; Costello *et al*., 2019b).

We recently performed a randomised controlled trial in 666 women with normogonadotropic anovulation and CC failure, in which we compared a switch to gonadotropins with continuing treatment with CC for another six cycles (Weiss *et al*., 2018). Switching to gonadotropins resulted in a cumulative live birth rate of 52% and continued ovulation induction with CC in a cumulative live birth rate of 41% (RR 1.24 [95% CI 1.05–1.46]; $P = 0.0124$). There were seven multiple pregnancies in the women treated with gonadotropins (2.1%) and eight in the women treated with CC (2.4%). The additional costs necessary to achieve one additional live birth in women treated with gonadotropins compared with CC was €15 258 (95% CI €8721 to €63 654) (Bordewijk *et al*., 2018).

It is unclear whether endometrial thickness (EMT) can be used to identify women who can continue on CC with similar live birth rates without the extra costs of gonadotropins. EMT seems a logical candidate biomarker since many studies have found evidence for negative effects of CC on the endometrium (Weiss *et al*., 2017, Gadalla *et al*., 2018).

The aim of this study was thus to evaluate whether EMT, during the sixth ovulatory cycle of ovulation induction with CC, can be used as biomarker to select between women with normogonadotropic anovulation and CC failure who are better off switching to gonadotropins and those who could continue CC.

Materials and Methods

Study design

We conducted a secondary analysis of the M-ovin study, a two-by-two factorial RCT, in 48 Dutch hospitals that compared live birth rates after ovulation induction with gonadotropins or CC with or without IUI in normogonadotropic anovulatory women with CC failure.

Ethical approval

Ethical approval was obtained by the Medical Ethical Committee of the Medical Spectrum Twente Enschede (Netherlands) and from the Central Committee on Research involving Human Subjects (CCMO, Netherlands). The board of directors of each of the participating centres approved local execution of the study. The original study was registered in the Netherlands Trial Register, number NTR1449.

Procedures

Details about the study design, sample size calculation, study procedures and outcomes have been described previously (Nahuis *et al*., 2013, Weiss *et al*., 2018). In summary, subfertile women of at least 18 years of age with normogonadotropic anovulation who had been ovulatory for six cycles on CC, but who had not conceived, were eligible for the trial. Couples with male subfertility and double-sided tubal pathology were not eligible. Consenting women were randomly allocated to six cycles of gonadotropins plus IUI, six cycles of gonadotropins plus intercourse, six cycles of CC plus IUI or six cycles of CC plus intercourse, on a 1:1:1:1 basis. We used a two-by-two factorial design to compare two pairs of interventions: a switch to ovulation induction with gonadotropins versus continuing CC and IUI versus intercourse.

Ovulation induction, cycle monitoring, semen preparation and insemination were performed according to local hospital protocols. The starting dose of gonadotropins was 50 or 75 IU daily, and participating clinics used either urinary or recombinant follicle stimulating hormone depending on their local protocol. Follicular

Table I Baseline characteristics of the women.

	Gonadotrophins *n* = 190	CC *n* = 190
Age of women (years)	29.8 (3.8)	29.8 (3.8)
Ethnicity		
White	157 (83%)	159 (82%)
Non-white	23 (12%)	21 (11%)
BMI (kg/m^2)	25.2 (5.4)	25.3 (4.7)
BMI > 25.0 kg/m^2	80 (42%)	81 (43%)
Current smoker	24 (13%)	20 (11%)
Diabetes	1 (0.5%)	4 (2.1%)
Previous live birth	42 (22%)	36 (19%)
Duration of subfertility (months)	25.3 (14.2)	24.3 (16.4)
Cycle pattern before treatment†		
Amenorrhoea	141 (74%)	145 (76%)
Oligomenorrhoea	32 (17%)	30 (16%)
Unknown	17 (8.9%)	15 (7.9%)
TMC ($\times 10^6$)	98 (158)	89 (127)
Polycystic ovaries on ultrasound‡	130 (68%)	138 (73%)
Mean serum biochemical values		
FSH (IU/L)	5.7 (1.9)	5.9 (2.1)
LH (IU/L)	10.5 (7.4)	10.9 (9.1)
Oestrogen (pmol/L)	259 (295)	229 (241)
Total testosterone (nmol/L)	1.6 (2.2)	1.6 (1.4)
Mid-cycle EMT	8.0 (2.3)	8.0 (2.5)
EMT > 7 MM	111 (58%)	107 (56%)

Data are mean (SD) or *n* (%). BMI = body mass index. TMC = total motile sperm count. FSH = follicle-stimulating hormone. LH = luteinising hormone. †Amenorrhoea: absence of menstrual bleeding for >6 months. Oligomenorrhoea: irregular menstrual bleedings with intervals of >35 days but ≤6 months. ‡Defined as the presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter.

growth was monitored by transvaginal ultrasound. We used 5000 IU of human chorionic gonadotrophin (hCG) to trigger ovulation. The dosage of CC ranged between 50 and 150 mg daily, for 5 days. If ovulation did not occur, the dosage was increased in steps of 50 mg with a maximum of 150 mg daily in the next cycles. Women undergoing ovulation induction with CC plus IUI were monitored by ultrasound, while women undergoing CC plus intercourse were monitored by basal body temperature curve, mid-luteal progesterone measurement or urinary luteal hormone surge depending on the local protocol.

The primary outcome measure was conception leading to live birth within eight months after randomisation. A live birth was defined as any baby born alive after a gestational age of 24 weeks. During the study, the data was collected by research nurses and after the last live birth, we closed the database. A secondary outcome was cost.

Mid-cycle EMT before randomisation

We collected data on mid-cycle EMT measured in the sixth cycle of ovulation induction with CC before randomisation. The ultrasound was planned to be pre-ovulatory according to local protocol. We started collecting this data after an amendment to the protocol. This amendment started after including 286 patients. The data was collected from the individual case report forms of the RCT. The EMT was measured by transvaginal ultrasound.

Statistical analysis

All analyses were performed for the outcome live birth rate. First, we tested for interaction of EMT with the treatment effect using logistic regression. Second, we performed a spline analysis to evaluate the association of EMT with chance of pregnancy leading to a live birth and to determine the best cut-off point. On basis of the resulting cut-off point, we calculated the relative risk and 95% CI of a live birth for gonadotropins versus CC at EMT values below and above this value. Third, we constructed Kaplan–Meier curves for time to conception leading to live birth for gonadotropins versus CC in relation to the cut-off value. The curves were compared with a log-rank test. A *P* value of less than 0.05 was considered to indicate statistical significance. Fourth, we analysed by logistic regression the EMT values over time for cycles 7 until 12 relative to the mid-cycle EMT of Cycle 6 determined in the women who received gonadotropins and the women who received CC. Fifth, we examined whether there was an association between live birth rates and different doses of CC. Sixth, we performed an economic analysis to determine the difference in

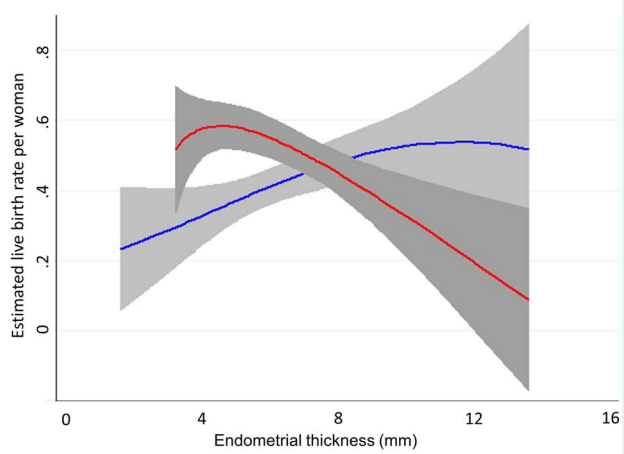

Figure 1 Spline function: interaction between endometrial thickness and treatment (gonadotropins and clomiphene citrate) on live birth. Red line: gonadotropins and blue line: clomiphene citrate.

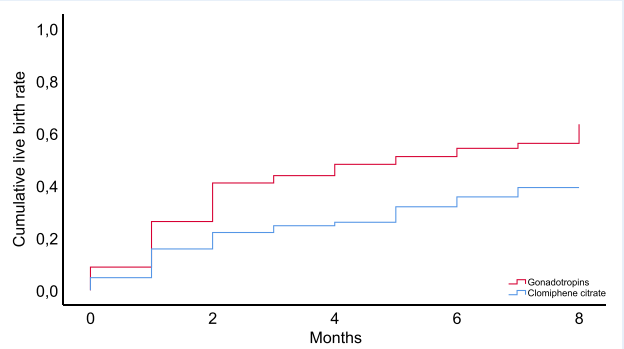

Figure 2 Kaplan–Meijer curve for live birth rate in women with an endometrial thickness ≤ 7. Time to conception leading to live birth for the comparison gonadotropins versus clomiphene citrate, and endometrial thickness ≤ 7 mm.

costs between gonadotropins and CC below and above the cut-off value using previously determined cost data (Bordewijk *et al.*, 2019). Costs were combined with effectiveness by calculating Incremental Cost-Effectiveness Ratios (ICER). SPSS software (version 23.0; IBM Corp., USA) was used for statistical analysis. STATA (Version 14.2; Stata Corp) was used for the spline analysis.

Results

Mid-cycle EMT before randomisation

Between 8 December 2008 and 16 December 2015, 666 women had been allocated to receive an additional six cycles with a change to gonadotropins ($N = 331$) or additional 6 cycles continuing with CC ($N = 335$). The mid-cycle EMT of the sixth CC cycle prior to randomisation was available in 380 women (57%), of whom 190 were

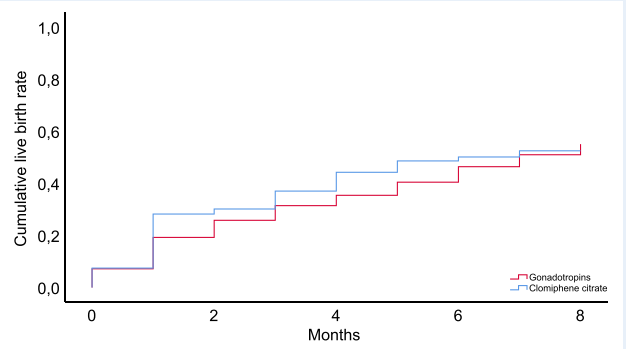

Figure 3 Kaplan–Meijer curve for live birth rate in women with an endometrial thickness > 7 mm. Time to conception leading to live birth for the comparison gonadotropins versus clomiphene citrate and an endometrial thickness EMT > 7 mm.

allocated to gonadotropins and 190 were allocated to CC. The baseline characteristics of the women in whom EMT had been measured were similar and are summarised in Table I. The values of EMT ranged from 2.0 to 20.4 mm.

There was an interaction between treatment and EMT on live birth ($P < 0.01$). The spline function clearly visualises the interaction between EMT and treatment on the outcome live birth and points towards a cut-off point at an EMT of 7 mm (Fig. 1). Among 162 women (45%) with EMT ≤ 7 mm, gonadotropins resulted in a live birth in 44 of 79 women (56%) and CC resulted in a live birth in 28 of 83 (34%) (RR 1.57, 95% CI 1.13–2.19). Among 218 women (55%) with EMT > 7 mm, gonadotropins resulted in a live birth in 53 of 111 women (48%) and CC resulted in a live birth in 52 of 107 women (49%) (RR 0.98, 95% CI 0.75–1.29).

For an EMT of ≤7, the mean time to conception leading to a live birth was 4.7 months (95% CI 4.0–5.4) following gonadotropins and 6.0 months (95% CI 5.4–6.6) following CC (log-rank test; $P = 0.008$; Fig. 2). For an EMT of >7, the mean time to conception leading to a live birth was 5.4 months (95% CI 4.9–6.0) following gonadotropins and 5.0 months (95% CI 4.4–5.6) following CC (log-rank test; $P = 0.56$; Fig. 3). The insemination method used, intercourse or IUI did not have any impact on either EMT values or live birth rates.

EMT during the course of treatment

Over time, the EMT increased slightly in the women who received gonadotropins. The EMT remained stable from Cycle 7 to Cycle 12 in the women who received CC (Fig. 4).

Dose of CC

There was no difference in live birth between women who received <100 mg CC (34/88) and women who received ≥100 mg CC (35/85) (RR 0.95, 95% CI 0.70–1.29). There was also no association between the dose of CC and the EMT values (Fig. 5).

Incremental cost-effectiveness

Mean direct medical costs per woman with EMT ≤ 7 mm receiving gonadotropins versus CC were €4873 versus €2778 (cost difference

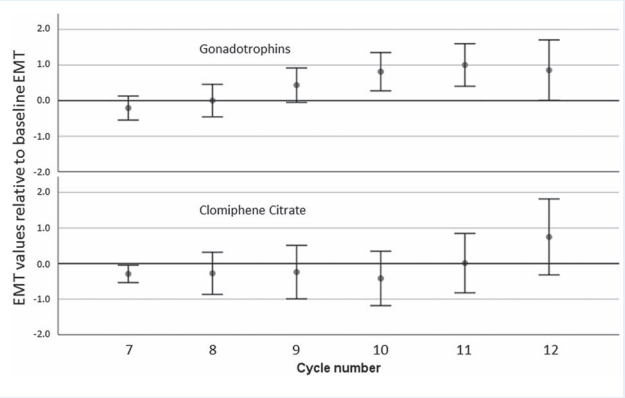

Figure 4 Endometrial thickness values of cycles 7 until 12 relative to the mid-cycle endometrial thickness of Cycle 6 over 6 cycles for gonadotropins and clomiphene citrate. Upper blot gonadotropins and lower blot clomiphene citrate. The dots represent the endometrial thickness mean difference. The lines represent the 95% confidence interval.

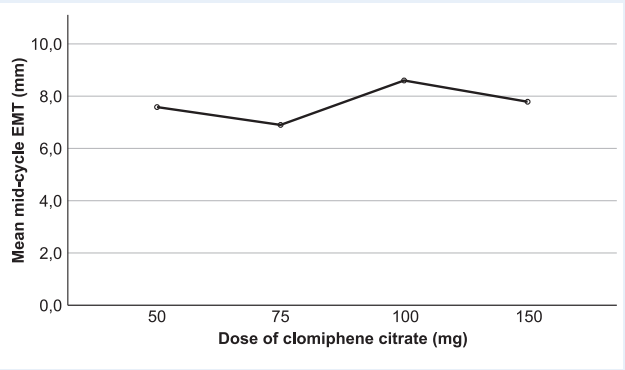

Figure 5 Dose of clomiphene citrate associated with the mean mid-cycle endometrial thickness.

of €2251 (95% CI: €2231–€2272)). The ICER was €9709 (95% CI: €5117 to €25 302) per additional live birth with gonadotropins (Supplementary Fig. S1).

Mean direct medical costs per woman with EMT > 7 mm receiving gonadotropins or CC were €4741 versus €3100 (cost difference of €1463 (95% CI: €1446–€1480)). The ICER estimates from the bootstrap analysis reflected greater costs for gonadotropins for similar effectiveness (Supplementary Fig. S2).

Discussion

In this study, we evaluated whether EMT can be used as a biomarker to select women with normogonadotropic anovulation who should switch to ovulation induction with gonadotropins and those who could continue on CC after six failed ovulatory cycles. A cut-off value of 7 mm was able to do so. In women with an EMT ≤ 7 mm in the sixth cycle, switching to gonadotropins improved live birth rate over continuing treatment with CC, at an extra cost of €9709 to achieve one additional live birth. In women with an EMT > 7 mm in the sixth cycle, continuing with CC produced similar live birth rates without the extra costs of gonadotropins.

A strength of our study is that the EMT measurements were performed in the context of a RCT by many different doctors performing the ultrasound measurements, enhancing both the internal validity and generalisability of the results. We investigated whether we had adequate power to perform this secondary study by calculating the power on basis of logistic regression with a binary independent variable (treatment) and a binary interacting variable (EMT). We had 83% power with our sample size of 380 women and 1:1 distributions of the variables.

A weakness of our study is that mid-cycle EMT measurements before randomisation during the sixth ovulatory CC cycle were not available for 286 of the women (43%) included in the original RCT. When the study started, we did not collect data on EMT in the case record forms, but the participating centres performed EMT measurements during treatment according to their local protocol as part of their routine monitoring. We added the EMT in the case record forms after the trial had included 286 women, and consequently, we only have EMT measurements of 380 women.

We believe this data has clinical implications, provided they are confirmed in future studies. Our original randomised trial showed that a switch of treatment to gonadotropins led to an absolute increase in live birth of 11% over treatment with CC in women with normogonadotropic anovulation and CC failure, while we here show that in women with an EMT ≤ 7 mm gonadotropins it leads to an absolute increase in live birth of 22% over continued treatment with CC. The additional cost necessary to achieve one additional live birth was calculated at €15 258 in the cost-effectiveness analysis of the original randomised trial (Weiss *et al.*, 2018, Bordewijk *et al.*, 2019). Consequently, the costs necessary to achieve one additional live birth in women with an EMT ≤ 7 mm are now lower at €9709. In women with an EMT > 7 mm, live birth rates were similar for those treated with gonadotropins and those who continued treatment with CC. Since gonadotropins are more expensive, CC should be the dominant strategy in women with an EMT > 7 mm.

The lower live birth rate with CC in women with an EMT smaller than 7 mm might be explained by the anti-estrogenic effects of CC on the endometrial development/receptivity, cervical mucus and uterine blood flow (Gadalla *et al.*, 2018). All women in this study had already had 6 cycles of CC. We hypothesise that the women with an EMT ≤ 7 mm in the sixth ovulatory cycle are more sensitive to the negative anti-estrogenic effect of CC on the endometrial receptivity, cervical mucus and uterine blood flow, resulting in an endometrium of lesser thickness and lesser receptiveness. The women with an EMT > 7 mm might be less sensitive to the anti-estrogenic effect of CC and are therefore able to produce a thick and good quality endometrium. The effect of CC appeared to be independent of CC dosage as higher doses had no effect on the measured EMT values, nor on the chance to a conception leading to a live birth. If women with an EMT ≤ 7 mm in the sixth ovulatory cycle switch to gonadotropins, there is no longer an anti-estrogenic of CC on the endometrium. From the spline analysis, no further inferences can be made on conception trends with decreasing or increasing EMT in the CC and FSH groups, due to the insecurity around the effect estimates at the more extreme EMT values. These previously described negative effects of CC may

explain in part why first line treatment with CC results in lower live birth rates than the aromatase inhibitor letrozole, as was summarised in an IPD meta-analysis (Wang *et al.*, 2019).

In women with normogonadotropic anovulation and six failed ovulatory cycles on CC and an EMT ≤ 7 mm in the sixth cycle, we advise switching to gonadotropins, since it improves live birth rate over continuing treatment with CC, at an extra cost of €9709 to achieve one additional live birth. If the EMT > 7 mm, we advise continuing treatment with CC, since live birth rates are similar to those with gonadotropins, but without the extra costs. This information can be used to update the guideline (https://www.monash.edu/medicine/sphpm/mchri/pcos/guideline).

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

P.G.H., F.v.d.V., B.W.J.M. and M.v.W. designed the trial. N.S.W. and M.J.N. were the trials coordinators. E.M.B. and N.S.W. were in charge of collecting the data. E.M.B. and M.v.W. performed the analyses. E.M.B. wrote the manuscript. J.K., A.F.L., G.A.v.U., F.P.J.V., B.J.C. and T.A.M.v.d.L.v.A. recruited and counselled participants of this study as local investigators. N.S.W., C.B.L., M.G., P.G.H., F.v.d.V., B.W.J.M. and M.v.W. helped with interpreting the outcomes of the data and reviewed the manuscript. All authors read, edited and approved the final manuscript.

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Conflict of interest

C.B.L.A. reports unrestricted grant support from Merck and Ferring. B.W.M. is supported by a NHMRC Practitioner Fellowship (GNT1082548) and reports consultancy for Merck, ObsEva, iGENOMIX and Guerbet. All other authors have nothing to declare.

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