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Maintenance of response to oral octreotide compared with injectable somatostatin receptor ligands in patients with acromegaly: a phase 3, multicentre, randomised controlled trial

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For the Russian translation of the abstract see Online for appendix 1

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Summary

Background Despite biochemically responding to injectable somatostatin receptor ligands (iSRLs), many patients with acromegaly experience treatment burdens. We aimed to assess maintenance of biochemical response and symptomatic control with oral octreotide capsules versus iSRLs in patients with acromegaly who previously tolerated and responded to both.

Methods This global, open-label, randomised controlled phase 3 trial was done in 29 clinical sites in Austria, France, Germany, Hungary, Italy, Lithuania, Russia, Serbia, Spain, and the USA. Eligible patients were adults aged 18–75 years with acromegaly who were receiving iSRLs (long-acting octreotide or lanreotide autogel) for at least 6 months before baseline with a stable dose for at least 4 months, and were deemed to be biochemically responding (insulin-like growth factor I [IGF-I] <1·3×upper limit of normal [ULN] and mean integrated growth hormone <2·5 ng/mL). In the 26-week run-in phase, all patients received oral octreotide (40 mg a day, optional titration to 60 or 80 mg a day). Eligibility for the randomised treatment phase was completion of the run-in phase as a biochemical responder (IGF-I <1·3×ULN and mean integrated growth hormone <2·5 ng/mL at week 24) and investigator assessment of acromegaly being adequately controlled. Patients were randomly assigned (3:2) to oral octreotide capsules or iSRL at the same dose and interval as before enrolment. Randomisation and drug dispensing were conducted through a qualified randomisation service provider (eg, interactive web or voice response system). The primary endpoint was a non-inferiority assessment (margin –20 percentage points) of proportion of participants maintaining biochemical response throughout the randomised treatment phase (IGF-I <1·3×ULN using time-weighted average; assessed by comparing the lower bound of the 2-sided 95% CI for the difference in biochemical response between groups). IGF-I was assessed once a month during the run-in and randomised treatment phases (single sample). Efficacy and safety assessments were performed on the randomised population. This trial is registered with ClinicalTrials.gov, NCT02685709.

Findings Between Feb 11, 2016, and Aug 20, 2020, 218 patients were assessed for eligibility. 72 patients were excluded, and 146 participants were enrolled into the run-in phase. 116 patients completed the run-in phase and 30 participants discontinued treatment. 92 participants were randomly assigned to oral octreotide (n=55) or iSRL (n=37). 50 (91%) of 55 participants who received oral octreotide (95% CI 44–53) and 37 (100%) of 37 participants who received iSRLs (34–37) maintained biochemical response. The lower bound of the 2-sided 95% CI for the adjusted difference in proportions between the two treatment groups achieved the prespecified non-inferiority criterion of –20% (95% CI –19·9 to 0·5). 19 (35%) of 55 participants in the oral octreotide group and 15 (41%) of 37 participants in the iSRL group had treatment-related adverse events; the most common of which in both groups were gastrointestinal.

Interpretation Oral octreotide was non-inferior to iSRL treatment, and might be a favourable alternative to iSRLs for many patients with acromegaly.

Funding Chiasma.

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Introduction

Current first-line standard of care for primary or adjuvant medical therapy in patients with acromegaly includes injectable somatostatin receptor ligands (iSRLs).[1,2] Pegvisomant, a growth hormone receptor antagonist, and cabergoline, a dopamine agonist, can also be used either as monotherapy or in combination with iSRLs.[3]

Treatment burden associated with iSRLs and medical treatment in general include injection site reactions, breakthrough acromegaly symptoms toward the end of injection interval, and inconvenience of administration.[4–11] Furthermore, patients often miss work if they have to travel to appointments for regular injections.[10] Oral octreotide is approved in the USA for the treatment of

Research in context

Evidence before this study

We searched PubMed for reports published at any date up to July 28, 2021, using the terms "oral octreotide" and "acromegaly". We included clinical trials in acromegaly and identified two phase 3 trials evaluating the efficacy and safety of oral octreotide. Oral octreotide was shown in phase 3 trials, both baseline and placebo-controlled, to maintain response consistently and effectively in patients who had previous biochemical control on injectable somatostatin receptor ligands (iSRLs).

Added value of this study

Our results build on previous studies of oral octreotide in acromegaly by incorporating a larger, global patient sample. Oral octreotide met the prespecified criterion for non-inferiority to iSRLs in maintaining biochemical response. Time-weighted average insulin-like growth factor-I (IGF-I) concentration was used as an integrated measure of efficacy across time that could limit the noise associated with normal variability in IGF-I concentrations. Patient-reported outcomes between treatments were also analysed for the first time, substantiating previously reported treatment burdens associated with iSRLs and the potential benefit of oral octreotide.

Implications of all the available evidence

Our results add to previous evidence of effective maintenance of biochemical response in patients with acromegaly when switching from iSRLs to oral octreotide, this time by direct comparison with the standard of care showing non-inferiority in those who have tolerated and responded to iSRLs and oral octreotide. Evidence from this trial further suggests that oral octreotide could mitigate some of the treatment burdens attributed to iSRL therapy in patients with acromegaly.

acromegaly in patients previously responding to and tolerating iSRLs (octreotide or lanreotide) and shows consistent and effective maintenance of biochemical response.[12,13]

We aimed to compare efficacy, safety, and patient-reported outcome measures in patients with acromegaly given oral octreotide and iSRLs.

Methods

Study design and participants

The Maintenance of acromegaly Patients with Octreotide capsules compared With injections–Evaluation of REsponse Durability (MPOWERED) study was a global, phase 3, randomised, open-label, active-controlled, multicentre trial that enrolled participants from 29 clinical sites in Austria, France, Germany, Hungary, Italy, Lithuania, Russia, Serbia, Spain, and the USA.

Eligible participants for the run-in phase were adults aged 18–75 years with acromegaly (documented evidence of a growth hormone-secreting pituitary tumour that was abnormally responsive to an oral glucose tolerance test or elevated insulin-like growth factor I (IGF-I; >1×upper limit of normal [ULN]) at any time in the past) who were currently receiving long-acting forms of octreotide or lanreotide iSRLs for at least 6 months with a stable dose for at least 4 months. At screening, participants must have been biochemical responders defined as IGF-I <1·3×ULN and mean integrated growth hormone <2·5 ng/mL over 2 h. Key exclusion criteria included an iSRL dosing interval longer than 8 weeks, previous participation in the CH-ACM-01 trial (NCT01412424), pituitary radiotherapy in the past 5 years, and pituitary surgery in the past 6 months. All participants provided written informed consent. This trial was conducted under Good Clinical Practice guidelines in accordance with the Declaration of Helsinki and United States Code of Federal Regulations, EU Directives, or local country regulations and guidelines. An independent ethics committee or institutional review board for each trial site approved the trial protocol.

Randomisation

The 62-week core trial consisted of screening, run-in, and randomised treatment phases (appendix 2 p 6). After screening, eligible participants entered a 26-week run-in phase in which all participants received oral octreotide to establish efficacious octreotide dose and to define the population of patients that had previously responded to and tolerated both oral octreotide and octreotide or lanreotide iSRLs. At week 26, responders (defined as those with IGF-I <1·3×ULN and mean integrated growth hormone <2·5 ng/mL at week 24 assessment, with investigator assessment of participants' acromegaly being adequately controlled) entered the 36-week randomised treatment phase. Eligible participants were randomly assigned (3:2) to oral octreotide or iSRLs using a centralised stratified randomisation based on week 24 assessments (IGF-I ≤1×ULN *vs* IGF-I >1 to <1·3×ULN and octreotide dose [40 mg *vs* 60 mg or 80 mg]). Randomisation and drug dispensing were conducted through a qualified randomisation service provider (eg, interactive web or voice response system). As the interventions were administered by different routes, masking was not possible.

Patients completing the core study were offered entry into an optional open-label extension of up to 5 years.

Procedures

The interval between the last iSRL treatment to baseline (first dose of oral octreotide in the run-in) could not exceed the routine dosing interval (by more than 3 days) from last injection. Patients could begin octreotide any

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See Online for appendix 2

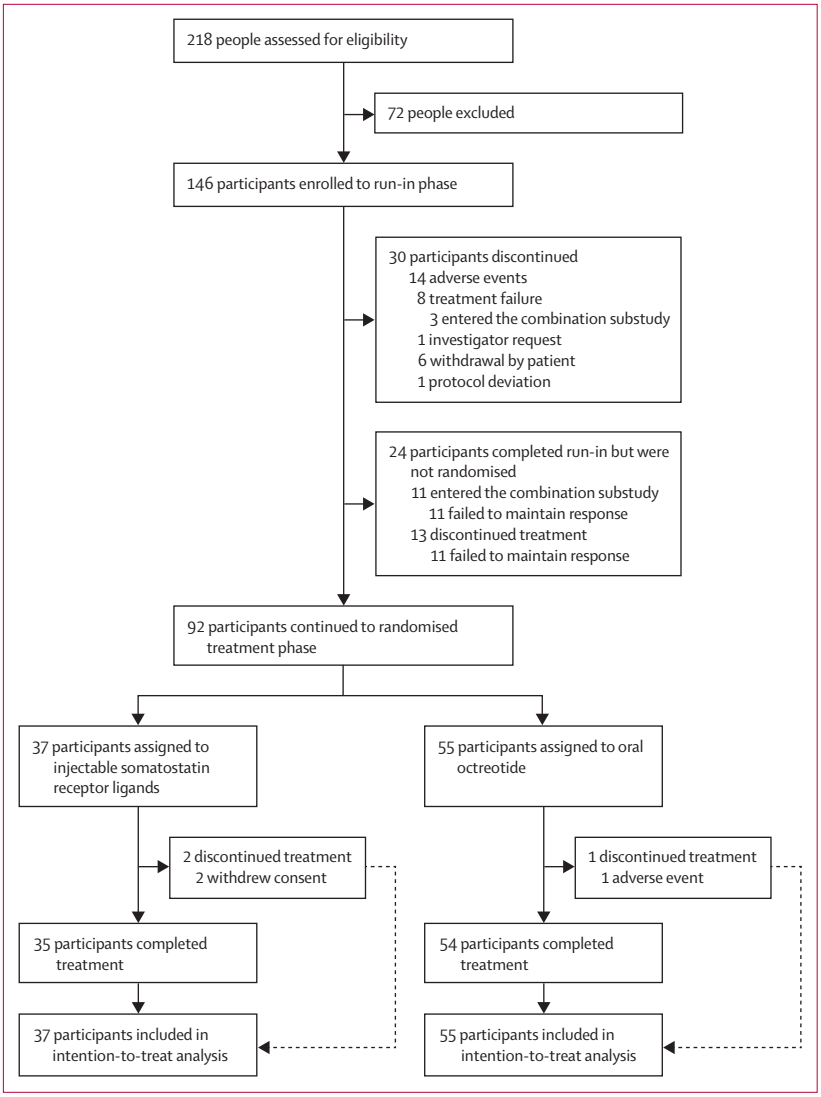

Figure 1: **Trial profile**

time within the dosing interval. Oral octreotide (OOC MYCAPSSA, Amryt Pharma; Dublin, Ireland) was given twice a day with a glass of water on an empty stomach (ie, ≥1 h before a meal or ≥2 h after a meal). Octreotide capsules were titrated during the run-in phase from 20 mg twice a day to 60 mg a day (40 mg in the morning, 20 mg in the evening) to 40 mg twice a day, by investigator discretion in the case of increased IGF-I, worsening acromegaly symptoms, or both.

Following randomisation, participants assigned to receive oral octreotide received the final dose achieved during the run-in phase. Participants randomly assigned to the active control group in the randomised treatment phase received their standard-of-care iSRL (octreotide LAR [Novartis, East Hanover, NJ, USA] or lanreotide autogel [Ipsen, Cambridge, MA, USA]) at the same dose and interval they received before trial enrolment.

IGF-I and growth hormone concentrations were measured by use of IDS-iSYS IGF-I (IS-3900; Immunodiagnostic Systems) and IDS-iSYS hGH (IS-3700; Immunodiagnostic Systems). IGF-I was assessed once a month during the run-in and randomised treatment phases (single sample). Average growth hormone concentration was assessed at screening and at the beginning and end of the run-in and randomised treatment phases (appendix 2 p 1).

Acromegaly active symptoms were assessed at every visit (at least once a month), per consensus guidelines designating acromegaly symptoms as a core clinical outcome in prospective trials evaluating new treatments. Symptom assessment included the Acromegaly Index of Severity (AIS) and acromegaly-directed physical examination (appendix 2 p 1).

Participants completed the Acromegaly Treatment Satisfaction Questionnaire (Acro-TSQ), a validated patient-reported outcome tool assessing overall convenience and satisfaction with treatment and patient perception of symptomatic control and adverse drug reactions (appendix 2 p 1),[7,14] at screening, baseline, end of run-in, and every 12 weeks during the randomised treatment phase, including the end of the randomised treatment phase. Work productivity was assessed via the Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP), a standardised and validated patient-reported outcome questionnaire that measures health-related impairment of work and regular activities (appendix 2 p 2).[15]

Outcomes

The primary efficacy endpoint was a non-inferiority assessment of proportion of participants maintaining biochemical response throughout the randomised treatment phase (IGF-I <1·3×ULN using time-weighted average); a longitudinal data analysis approach intended to provide a clinically meaningful endpoint of IGF-I control over a long period of time,[16–19] accounting for natural variation in IGF-I during the study period.[20–22]

A sensitivity analysis was performed on the primary endpoint evaluating participants who were biochemical responders at the start of the randomised treatment phase (week 26). Exploratory landmark analyses assessed the proportion of participants with IGF-I <1·3×ULN at the end of the randomised treatment phase (based on average of week 58 and 62) in all randomly assigned patients and responders at the start of the randomised treatment phase.

Secondary endpoints were analysed without adjustment for multiplicity or predefined non-inferiority margins and therefore were interpreted as exploratory. Key secondary biochemical endpoints included change in IGF-I and change in mean integrated growth hormone from the start of the randomised treatment phase (week 26) until the end of the randomised treatment phase (week 62). Key symptomatic endpoints included number of

symptoms per patient, mean AIS score at baseline compared with end of run-in, proportion of patients with each symptom, and proportion of participants who maintained or reduced the overall number of active acromegaly symptoms at randomised treatment phase end compared with start of the randomised treatment phase. Patient-reported outcome endpoints included changes in Acro-TSQ domain scores in the run-in phase, overall effect on Acro-TSQ in the randomised treatment phase, and WPAI:SHP scores from the end of run-in compared with baseline and from start to end of the randomised treatment phase. Efficacy endpoints and populations analysed are comprehensively summarised in the appendix 2 (p 3).

Safety variables and assessments included adverse events, abdominal (gallbladder) ultrasonography, echocardiogram, and laboratory assessment. Treatment-emergent adverse events were adverse events with an onset on or after study drug initiation at run-in (day 0) or an adverse event that worsened in severity after the first dose of study drug and before the last dose of study drug.

Statistical analysis

The trial planned to enrol approximately 80 participants (with a 3:2 ratio) in the randomised treatment phase, with approximately 48 participants assigned to the oral octreotide group and 32 to the iSRL group. The sample size was selected to provide at least 70% power to show non-inferiority between oral octreotide and iSRL with a non-inferiority margin of –20% and a 2-sided 5% significance level, assuming a response rate to oral octreotide of at least 90% and a response rate to iSRLs of at least 95%.

Assessment of non-inferiority was made by comparing the lower bound of the 2-sided 95% CI for the difference in biochemical response (oral octreotide–iSRL) with the predefined non-inferiority margin of –20 percentage points, which was selected on the basis of previous publications that reported maintenance of response to injectable SRLs was observed in 80% to 90% of patients.[23–26] The stratified Miettinen & Nurminen method[27,28] with Cochran–Mantel–Haenszel weighting was used to estimate the difference in response rates for the primary endpoint between oral octreotide and iSRLs and the associated 2-sided 95% CIs. We report number and percentage of participants in each category for categorical variables. For continuous variables, descriptive statistics included number of participants (n), mean, SD, median, 25th percentile, 75th percentile, minimum, and maximum. All analyses were performed with Statistical Analysis System version 9.4.

Baseline assessments and efficacy analyses for both the run-in and the randomised treatment phase were performed on the full analysis set (n=92), all randomly assigned participants in the randomised treatment phase. Sensitivity analysis was performed on participants who were biochemical responders at start of the randomised treatment phase (week 26, n=84). Safety assessments were performed on the population of randomly assigned participants who received at least one dose of study drug during the randomised treatment phase. Analyses of

	Oral octreotide (n=55)	iSRL (n=37)
Age, years	54·1 (10·9)	55·2 (8·8)
Sex		
Male	20 (36%)	11 (30%)
Female	35 (64%)	26 (70%)
Race		
Black/African or African American	2 (4%)	0
White	49 (89%)	35 (95%)
Other	4 (7%)	2 (5%)
Ethnicity		
Hispanic or Latino	1 (2%)	2 (5%)
Not Hispanic or Latino	50 (91%)	33 (89%)
Not reported	4 (7%)	2 (5%)
BMI at screening, kg/m^2	28·8 (4·8)	28·5 (4·5)
Duration of acromegaly		
<10 years	22 (40%)	23 (62%)
10 to <20 years	26 (47%)	10 (27%)
≥20 years	7 (13%)	4 (11%)
Pituitary tumour type		
Microadenoma	13 (24%)	11 (30%)
Macroadenoma	40 (73%)	26 (70%)
Other	2 (4%)	0 (0)
Residual tumour size		
No remnants	24 (44%)	21 (57%)
<5 mm	12 (22%)	8 (22%)
5–10 mm	13 (24%)	3 (8%)
>10 mm	6 (11%)	5 (14%)
Previous acromegaly treatments		
Surgery only	35 (64%)	25 (68%)
Radiotherapy only	1 (2%)	0 (0)
Surgery and radiotherapy	10 (18%)	7 (19%)
Neither surgery nor radiotherapy	9 (16%)	5 (14%)
IGF-I		
≤1 × ULN	37 (67%)	29 (78%)
>1 to <1·3 × ULN	12 (22%)	8 (22%)
≥1·3 × ULN	6 (11%)	0 (0)
IGF-I x ULN	0·9 (0·35)	0·8 (0·21)
Previous iSRL treatment		
Low*	10 (18%)	9 (24%)
Middle†	19 (35%)	14 (38%)
High‡	26 (47%)	14 (38%)

Data are n (%) or mean (SD). IGF-I=insulin-like growth factor I. iSRL=injectable somatostatin receptor ligand. ULN=upper limit of normal. *Any octreotide dose less than 20 mg total per month or lanreotide less than 90 mg total per month. †Any octreotide dose less than 30 mg total per month or lanreotide less than 120 mg total per month. ‡Any octreotide dose 30 mg or higher total per month or lanreotide 120 mg or more total per month.

Table 1: **Baseline characteristics at start of randomised treatment phase**

	Oral octreotide (n=55)	iSRL (n=37)	Adjusted difference in proportions
Primary endpoint			
Biochemical responders in randomised treatment phase (TWA)	50 (91%, 44–53)	37 (100%, 34–37)	−9·1% (−19·9 to 0·5)
Key exploratory endpoints			
Landmark analysis of biochemical response at end of RCT	49 (89%, 43–53)	35 (95%, 30–37)	−5·5% (−17·7 to 7·9)
Population with maintained or reduced number of acromegaly symptoms in randomised treatment phase*	41 (75%, 34–47)	26 (70%, 20–31)	4·6% (−13·6 to 23·9)
Sensitivity analyses			
Population of responders at start of randomised treatment phase	n=48	n=36	NA
Proportion of biochemical responders in randomised treatment phase (TWA)	46 (96%, 47–55)	36 (100%, 33–37)	−3·8% (−14·7 to 5·0)
Landmark analysis of biochemical responders at end of randomised treatment phase*	45 (94%, 46–55)	34 (94%,30–37)	−1·6% (−13·8 to 11·7)

Data are n, n (%, 95% CI), or % (95% CI). Biochemical response defined as IGF-I less than 1·3 × ULN. All secondary endpoints are categorised as exploratory. iSRL=injectable somatostatin receptor ligand. TWA=time-weighted average. IGF-I= insulin-like growth factor I. NA=not applicable. *Landmark analysis assessed the proportion of participants with IGF-I less than 1·3 × ULN at the end of the randomised treatment phase (based on average of week 58 and 62 values) using non-response imputation procedure that regarded any participants who discontinued the randomised treatment phase early for any reason as non-responders.

Table 2: **Primary endpoint and key exploratory endpoints**

safety and efficacy data collected in the substudy evaluating cabergoline in combination with oral octreotide were performed in the combination analysis set, consisting of all patients who were enrolled in the substudy (n=14; appendix 2 p 3).

A steering committee acted in an advisory capacity to the Sponsor to provide oversight to the trial conduct and to support its successful completion. An independent data monitoring committee acted in an advisory capacity to the Sponsor to monitor participant safety during the trial. This trial is registered with ClinicalTrials.gov, NCT02685709.

Role of the funding source

The study sponsor designed the trial in collaboration with a committee of investigators, provided funding and organisational support, collected data, performed the analyses in alignment with the prespecified statistical analysis plan, and had a role in the data interpretation and writing of this Article through medical writing support.

Results

Between Feb 11, 2016, and Aug 20, 2020, 218 patients were assessed for eligibility. 72 patients were ineligible, and 146 eligible participants were enrolled into the run-in phase and received at least one dose of oral octreotide study drug. Of these, 116 (80%) completed the run-in phase, and 30 (20%) discontinued treatment (figure 1). The most common reasons for discontinuation were treatment-emergent adverse events (TEAEs; 14 [9·6%] of 146 patients) and treatment non-response (eight [5·5%] of 146 patients, three of whom entered the combination phase). Of the 116 patients who completed the run-in phase, 92 (79%) entered the randomised treatment phase as biochemical responders (IGF-I <1·3×ULN and mean integrated growth hormone <2·5 ng/mL at week 24). 55 participants were randomly assigned to oral octreotide and 37 participants were randomly assigned to iSRLs. 24 participants completed the run-in phase but were not randomised (11 entered the combination substudy and 13 did not continue treatment). Final oral octreotide dose during the run-in phase for randomly assigned patients was 40 mg in 39 participants, 60 mg in 25 participants, and 80 mg in 28 participants. Of the 92 participants who entered the randomised treatment phase, 89 (97%) completed treatment, with two discontinuations in the iSRL group (both withdrew consent) and one in the oral octreotide group (adverse event). Of those who completed the randomised treatment phase, 52 chose to continue into the trial extension (34 [63%] of 54 patients in the oral octreotide group and 18 [51%] of 35 patients in the iSRL group).

Participants in the two groups in the randomised treatment phase were well balanced for age, sex, and acromegaly duration, with noticeable differences in number of patients with IGF-I at least 1·3×ULN at week 26 (table 1). At the start of the randomised treatment phase (week 26), six participants randomly assigned to oral octreotide had an IGF-I of 1·3×ULN or higher and none of the participants randomly assigned to the iSRL group had an IGF-I of 1·3×ULN or higher. In addition, a greater proportion of patients in the oral octreotide group received high iSRL doses before baseline than did patients in the iSRL group (26 [47%] of 55 *vs* 14 [38%] of 37), and a greater proportion of patients in the oral octreotide group had tumour remnants on magnetic resonance imaging than the iSRL group (31 [56%] of 55 *vs* 16 [43%] of 37).

For the primary efficacy endpoint, 50 (91%) of 55 participants who received oral octreotide (95% CI 44–53) and 37 (100%) of 37 participants who received iSRLs (34–37) maintained biochemical response. The lower bound of the 2-sided 95% CI for the adjusted difference in proportions between the two treatment groups achieved the prespecified non-inferiority criterion of –20% (95% CI –19·9 to 0·5; table 2).

In a sensitivity analysis of the primary endpoint that evaluated time-weighted average response throughout the randomised treatment phase in participants who entered the randomised treatment phase as responders, 46 (96%) of 48 participants receiving oral octreotide (95% CI 47–55) and 36 (100%) of 36 participants in the iSRL group (33–37) maintained response during the randomised treatment phase (difference –3·8%, 95% CI –14·7 to 5·0; table 2). Landmark analysis of response at

the end of the randomised treatment phase was done by use of non-response imputation, which defined participants who discontinued in the randomised treatment phase for any reason as treatment non-response. Among all patients randomly assigned in the randomised treatment phase, 49 (89%) of 55 participants in the oral octreotide group (95% CI 43–53) and 35 (95%) of 37 in the iSRL group (30–37) maintained response at the end of the randomised treatment phase (difference –5·5%, 95% CI –17·7 to 7·9). In a landmark analysis of participants who entered the randomised treatment phase as responders, 94% of both groups (oral octreotide 45 of 48 participants, 95% CI 46–55; iSRL 34 of 36 participants, 30–37) were biochemical responders in the randomised treatment phase (difference –1·6%, 95% CI –13·8 to 11·7; table 2). All sensitivity analyses met the non-inferiority criterion for the primary endpoint.

IGF-I was stable in the randomised treatment phase in both groups. Mean IGF-I was the same at the start and end of the randomised treatment phase in both groups (0·9 [SD 0·35]×ULN in the oral octreotide group and 0·8 [0·22]×ULN in the iSRL group; appendix 2 p 7). Least squares mean change in growth hormone from the start of randomised treatment phase to the end of randomised treatment phase was –0·03 ng/mL (95% CI –0·24 to 0·19) in the oral octreotide group and 0·3 ng/mL (0·02–0·55) in the iSRL group (appendix 2 p 7).

Although the size of the trial made subgroup analyses difficult, we analysed baseline characteristics as predictors of response. Patients with baseline IGF-I within normal limits were more likely to enter the randomised treatment phase compared with patients with baseline IGF-I 1–1·3×ULN (p=0·0005). We did not identify any other predictors of response to oral octreotide.

The overall number of individual active acromegaly symptoms at the end of the randomised treatment phase were similar between the treatment groups (figure 2A). 41 (75%) of 55 participants in the oral octreotide group (95% CI 34–47) and 26 (70%) of 37 participants in the iSRL group (20–31) maintained or reduced their overall number of active acromegaly symptoms at the end of the randomised treatment phase compared with start of the randomised treatment phase (table 2).

Change from start of randomised treatment phase for each of the Acro-TSQ scales was generally similar between treatment groups (appendix 2 p 8). For treatment convenience, significantly greater deterioration was found in the iSRL group than in the oral octreotide group during the randomised treatment phase (p=0·04; figure 3A).

8 (15%) of 53 participants in the oral octreotide group had breakthrough symptoms at the end of the randomised treatment phase, compared with 11 (31%) of 36 participants in the iSRL group. 17 (47%) of 36 participants randomly assigned to iSRL reported injection site reactions via the Acro-TSQ at the end of the randomised treatment phase, and 13 (81%) of 16 reported

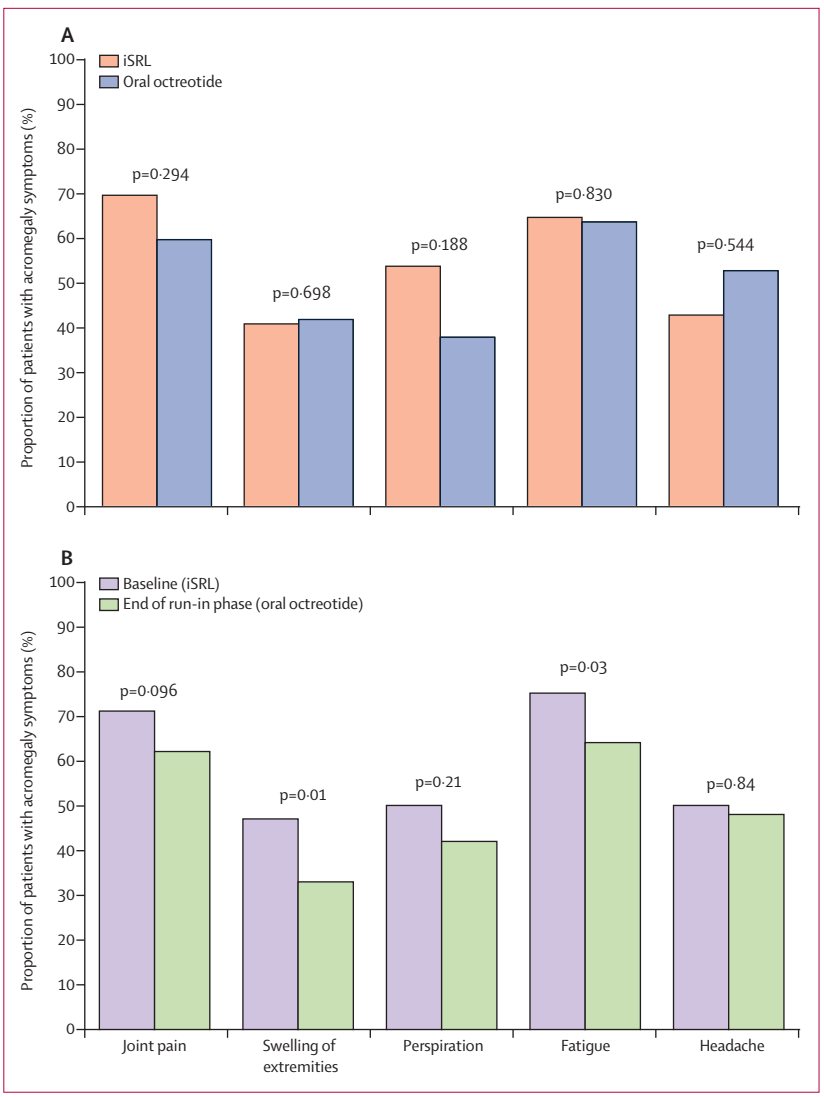

Figure 2: **Proportion of patients with individual acromegaly symptoms**
(A) End of randomised treatment phase. (B) Baseline and end of run-in phase. iSRL=injectable somatostatin receptor ligand.

that injection site reactions interfered with daily activities. Data were not available for one participant.

WPAI:SHP baseline data were similar between the oral octreotide and iSRL groups. At the end of the randomised treatment phase, scores were similar between treatment groups (data not shown).

An assessment of oral octreotide in combination with cabergoline showed that IGF-I at week 36 improved in most patients with combination treatment despite loss of response on oral octreotide alone (appendix 2 p 10).

The overall exposure to octreotide monotherapy in MPOWERED was 192·7 patient years. During the randomised treatment phase, the mean duration of study drug exposure was 36·0 weeks (SD 4·1) in the oral octreotide group (range 7·6–42·1) and 36·0 weeks (3·6) in the iSRL group (24·6–42·3). Safety in the run-in phase of

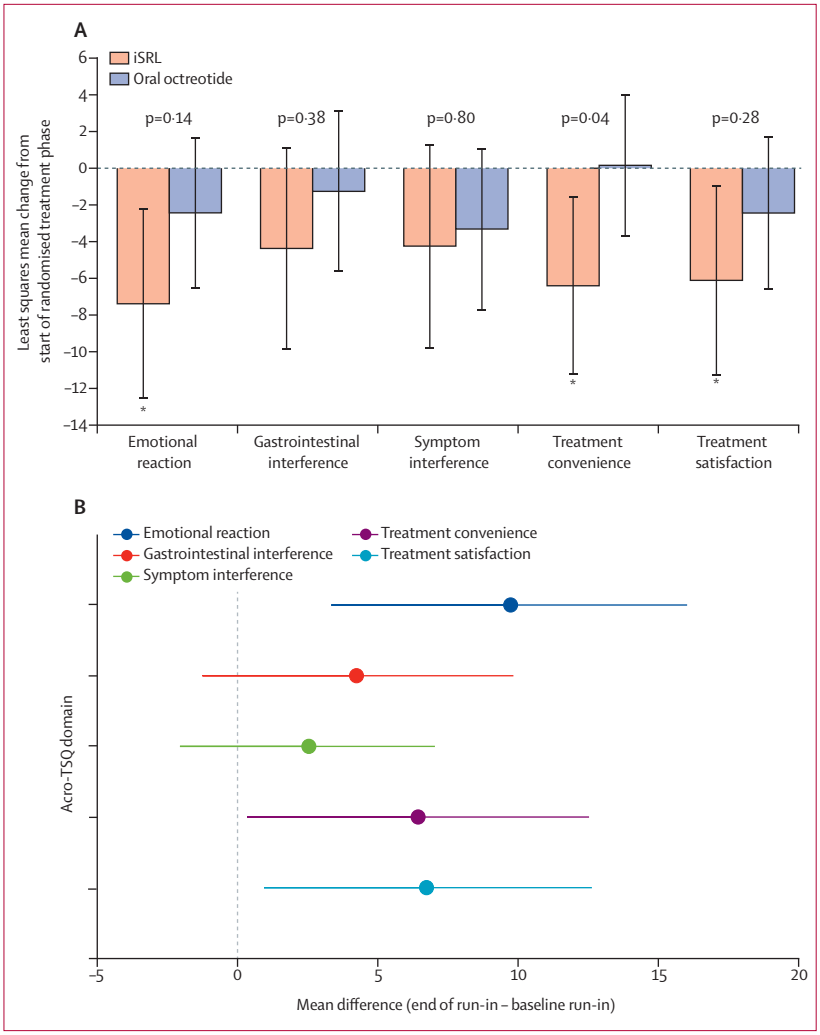

Figure 3: **Overall effect in Acro-TSQ domains in the randomised treatment and run-in phases**
(A) Least squares mean change in Acro-TSQ score from start of randomised treatment phase (B) Overall effect in Acro-TSQ domains in the run-in phase. Lower scores represent higher burden or lower satisfaction for each scale. Data are the average of the changes from randomised treatment phase baseline to each randomised treatment phase visit during which Acro-TSQ was assessed (weeks 38, 50, and 62 [end of randomised treatment phase]). Data on Acro-TSQ from the randomised treatment phase are found in the appendix (p 8). p values denote significant changes between the groups. Error bars indicate 95% CI. Acro-TSQ=Acromegaly Treatment Satisfaction Questionnaire. iSRL=injectable somatostatin receptor ligand. *Significant change within group from start of the randomised treatment phase (while patients were given oral octreotide) to each randomised treatment phase visit.

	Oral octreotide (n=55)	iSRL (n=37)	Overall (n=92)
TEAEs	123	128	251
Participants with ≥1 TEAE	39 (71%)	26 (70%)	65 (71%)
SAEs	5	3	8
Participants with ≥1 SAE	3 (6%)	3 (8%)	6 (7%)
Participants with ≥1 moderate TEAE	16 (29%)	8 (22%)	24 (26%)
Participants with ≥1 severe TEAE	5 (9%)	4 (11%)	9 (10%)
Participants with ≥1 treatment-related TEAE*	19 (35%)	15 (41%)	34 (37%)
Participants with TEAEs leading to study drug discontinuation	1 (2%)	0 (0)	1 (1%)
Deaths	1 (2%)	0 (0)	1 (1%)
Treatment-related TEAEs (≥5% in either treatment group) by system organ class and preferred term			
Gastrointestinal disorders	17 (31%)	9 (24%)	26 (28%)
Flatulence	10 (18%)	6 (16%)	16 (17%)
Nausea	9 (16%)	1 (3%)	10 (11%)
Diarrhoea	4 (7%)	5 (14%)	9 (10%)
Abdominal pain	3 (6%)	2 (5%)	5 (5%)
Constipation	1 (2%)	3 (8%)	4 (4%)
General disorders and administration site conditions	0 (0)	8 (22%)	8 (9%)
Injection site nodule	0 (0)	5 (14%)	5 (5%)
Injection site pain	0 (0)	3 (8%)	3 (3%)
Pain	0 (0)	2 (5%)	2 (2%)
Skin and subcutaneous tissue disorders	0 (0)	4 (11%)	4 (4%)
Erythema	0 (0)	4 (11%)	4 (4%)

Data are n or n (%). TEAEs were defined as adverse events with an onset on or after study drug initiation and before the end of treatment in the randomised treatment phase. Adverse events were coded using MedDRA, version 18.1. iSRL=injectable somatostatin receptor ligand. SAE=serious adverse event. TEAE=treatment-emergent adverse event. *An adverse event was considered related if the relationship to study drug was reported as possibly related or related.

Table 3: **Adverse events during randomised treatment phase**

the trial was similar to that in previously published results of patients switching from iSRLs to oral octreotide (appendix 2 p 4). The incidence of TEAEs during the randomised treatment phase was similar between groups, with 39 (71%) of 55 participants in the oral octreotide group and 26 (70%) of 37 participants in the iSRL group reporting at least one TEAE. A full summary of TEAEs by system organ class (≥5% incidence in either group) is provided in the appendix 2 (p 5). 19 (35%) of 55 participants in the oral octreotide group and 15 (41%) of 37 participants in the iSRL group had treatment-related TEAEs. Occurrence was similar for serious adverse events (AEs; oral octreotide three [6%] of 55 and iSRL three [8%] of 37) and severe AEs (oral octreotide five [9%] of 55 and iSRL four [11%] of 37; table 3). One participant in the oral octreotide group did not complete the randomised treatment phase because of an unrelated fatal AE (accidental death from combined drug poisoning with toxicology positive for ethanol, caffeine, cocaine, benzoylecgonine, and oxycodone). No new or unexpected safety signals were identified.

In both treatment groups, most treatment-related TEAEs were gastrointestinal. The most common gastrointestinal TEAEs related to study drug were flatulence (oral octreotide ten [18%] of 55 and iSRL six [16%] of 37), nausea (oral octreotide nine [16%] of 55 and iSRL one [3%] of 37), diarrhea (oral octreotide four [7%] of 55 and iSRL five [14%] of 37), abdominal pain (oral octreotide three [6%] of 55 and

iSRL two [5%] of 37), and constipation (oral octreotide one [2%] of 55 and iSRL three [8%] of 37; table 3).

Adverse events of interest included cholelithiasis (oral octreotide 0 and iSRL one [3%, categorised as serious] of 37) and secondary hypothyroidism (oral octreotide one [2%, mild intensity and deemed unrelated to study drug] of 55 and iSRL 0). In the iSRL group, 12 (32%) of 37 participants spontaneously reported injection site reactions; ten (27%) of 37 participants reported during the randomised treatment phase (six injection site nodules, four injection site pain, and one injection site erythema [some reactions were reported in the same patient]); and two (5%) of 37 participants reported as part of the acromegaly-directed physical examination (one nodule and one pain and haematoma).

Of the 146 enrolled patients, 94 (64%) were biochemical responders at the end of the run-in (average of week 24 and 26) and 92 enrolled in the randomised treatment phase, representing the population of patients intended for long-term maintenance with oral octreotide.

In 92 patients who responded to oral octreotide, a statistically significant reduction was noted in the number of active acromegaly symptoms per patient from baseline to the end of run-in phase, and AIS scores (reflecting both the number and severity of symptoms) improved over time (appendix 2 p 9). Among active acromegaly symptoms, there were statistically significant reductions in the proportions of participants with swelling of extremities (p=0·01) and fatigue (p=0·03), but no differences were seen in joint pain, headache, or perspiration (figure 2B).

Patients who responded to oral octreotide and were randomly assigned in the randomised treatment phase showed significant improvement from baseline (when receiving iSRLs) to the end of run-in (when receiving octreotide) in three of the five Acro-TSQ scales (emotional reaction, treatment convenience, and treatment satisfaction), with trends in the other two scales (gastrointestinal interference and symptom interference; figure 3B). The sixth Acro-TSQ domain (injection site interference) could not be compared between end of run-in (while receiving octreotide) and baseline (while receiving iSRL), as patients given oral octreotide did not receive injections. Among participants responding to oral octreotide, breakthrough symptoms were reported less frequently at the end of the run-in phase than at baseline (four [7%] of 57 while receiving oral octreotide and 14 [25%] of 57 while receiving iSRLs). In responders, WPAI:SHP showed significant improvements in presenteeism (least squares mean –6·65, 95% CI –12·39 to –0·90; p=0·024), work productivity loss (–6·92, –12·83 to –1·02; p=0·022), and activity impairment (–4·94, –9·17 to –0·71; p=0·022) at the end of run-in phase when given oral octreotide compared with baseline when given iSRLs.

Discussion

Oral octreotide met the primary efficacy endpoint, showing similar maintenance of biochemical response with oral octreotide and iSRLs in participants with acromegaly previously responding to and tolerating both treatments.

Oral octreotide was non-inferior to iSRLs in maintaining biochemical response by use of the time-weighted average analysis, a clinically relevant measure of IGF-I that represents an integrated measure of efficacy across time[16–19] and can limit the noise associated with high variability in IGF-I.[20–22] Sensitivity analyses showed that the primary efficacy analysis is robust and supports the conclusion of non-inferiority. The strength of the outcomes is bolstered by the fact that oral octreotide met the primary non-inferiority endpoint despite clinical characteristics suggestive of more active disease in the oral octreotide group at baseline, with greater proportions of patients in this group having IGF-I values of 1·3×ULN or higher at randomised treatment phase baseline, receiving higher iSRL doses before trial baseline, and having larger tumour remnants on MRI at trial baseline. Biochemical control was maintained in 64% of patients receiving oral octreotide at the end of the run-in phase, a rate similar to that observed in previous studies of oral octreotide.[12,13] These rates support those seen in other studies assessing maintenance of response with long-acting iSRLs in patients who previously responded to injections.[29–31] Furthermore, the high maintenance of response in the oral octreotide group throughout the randomised treatment phase is consistent with results from the two earlier phase 3 studies of octreotide, in which 85% and 92% of patients who had responded at the end of dose titration maintained response at 9 months or later.[12,13]

Although non-inferiority was assessed on the basis of the randomised treatment phase, symptom and patient-reported outcome data in this phase were not powered for statistical comparisons. Similar symptom control and patient-reported outcome findings were reported between oral octreotide and iSRL treatment groups in the randomised treatment phase. The design of the trial meant that data collected from the run-in phase could be used to provide insights into symptomatic control and patient-reported outcomes within the intended target population—those showing response on oral octreotide. In this group, oral octreotide resulted in significant improvement in both number and severity of acromegaly symptoms. Of note, significantly fewer patients who responded to oral octreotide had extremity swelling and fatigue while receiving oral octreotide in the run-in phase. Headaches occurred in similar rates at the start and end of run-in, which suggests that symptomatic control of headaches was maintained. These observations support previous results, in which participants who switched to oral octreotide from iSRLs showed a significant reduction in joint pain, extremity swelling, and fatigue.[12] In this population of patients who biochemically responded to oral octreotide, patient-reported outcomes were also improved at the end of the run-in phase (when patients were receiving oral octreotide) compared with baseline (when patients were receiving iSRLs). A limitation of the

patient-reported outcome analyses is that patients chose to participate in this trial, so the enrolled population might be enriched for those who are unsatisfied with their current injectable therapy.

The patient-reported outcome results from this study substantiated, with a validated tool,[14] the previously reported treatment burdens associated with iSRLs[7,9,10,32,33] and allowed for an assessment of how patients who responded to oral octreotide treatment might avoid some of these burdens. In this trial, patients showing response to treatment with oral octreotide reported improved patient satisfaction, convenience, and emotional wellbeing, and decreased breakthrough symptoms. Three of the four WPAI:SHP scores (presenteeism, work productivity loss, and activity impairment) significantly improved in these patients during the run-in phase, showing a better work efficiency with oral octreotide treatment in patients showing response on oral octreotide. Satisfaction with oral octreotide treatment was high, and despite a long trial with a demanding trial design and several shifts in treatment, 63% of participants chose to continue into the extension and receive oral octreotide.

The oral octreotide safety profile is consistent with the known safety profile of injectable octreotide and the disease burden of acromegaly without injection site reactions. Although the trial did not monitor tumour control, no AEs were reported that suggest any change in pituitary tumour status. Nausea was more frequently reported with oral octreotide versus iSRLs, but overall numbers were small and no participants discontinued treatment in the randomised treatment phase due to nausea. Although long-acting iSRLs are prescribed for most patients as first-line treatment,[1,2] many patients with acromegaly report AEs from iSRLs as well as persistent symptoms of disease burden.[1,8] Indeed, 85% of participants in one trial[9] expressed interest in an alternative form of treatment that would avoid the need for injection. In our study, 47% of participants who received iSRLs reported injection site reactions as part of Acro-TSQ, and 81% of patients stated that these symptoms interfered with daily activities. As an oral option for the treatment of acromegaly, oral octreotide helps to address an unmet need in some patients by reducing the burden associated with injections, including better symptom control and elimination of injection site reactions.[7,9,10,32]

Strengths of this trial include that it was a multicentre, international enrolment trial with long-term assessments over 15 months. Endpoints were assessed using central laboratory assays and with several formal assessments of validated patient-reported outcomes. The results showed non-inferiority despite imbalance in some of the major characteristics apparent at the start of the randomised treatment phase. Oral octreotide requires twice-daily dosing and must be taken apart from meals. Although proton pump inhibitor therapy can affect oral octreotide absorption,[34] it is important to note that use of proton pump inhibitors was not an exclusion criterion in this study, and results therefore represent patients regardless of their use. This trial has several limitations, including the difficulty in recruiting for clinical trial of an orphan disease, the number of participants who did not continue into the randomised treatment phase, and the rigid criteria that participants who were randomly assigned must have responded to and tolerated both iSRL and oral octreotide. All of these factors limited the number of participants who were able to enter the randomised treatment phase. Another limitation was that the trial was not powered to report non-inferiority or superiority between arms for symptoms and patient-reported outcomes, and the findings could only suggest a trend, given the observed variability of each tool. However, these measures were assessed using within-patient analyses in the run-in phase of the trial.

We report maintenance of response in patients with acromegaly who received oral octreotide who previously tolerated and had biochemical response on both oral octreotide and standard of care iSRL treatment. Given these observed outcomes, oral octreotide could be a favourable alternative to iSRLs for many patients with acromegaly.

Contributors

This trial was designed by the sponsor, Chiasma, (acquired by Amryt Pharmaceuticals as of August, 2021), in discussion with investigators, who endorsed the study design. WHL, GP, AH, MF, and SM contributed to the conceptualisation of the study. YG-S and AH performed data curation and formal analysis, and verified the data. MF, AD, IB, GV, DM, YGP, NL, GR, EG, and YEP were investigators in the study. YG-S, WHL, and AH contributed to methods, project administration, and visualisation. MF, YG-S, WHL, GP, AH, NRB, SM, and CJS provided supervision of the study. MF, YG-S, WHL, and AH developed the original draft of this manuscript and MF, AD, IB, GV, DM, YGP, MEM, NL, GR, EG, YEP, YG-S, WHL, GP, AH, MBG, NRB, SM, and CJS critically reviewed and edited the manuscript, had access to the data on request, and made the final decision to submit for publication. Medical writing assistance and revision of the outline and manuscript under the direction of the authors was provided by PRECISIONscientia and compensated by Chiasma. All authors had full access to the trial data, and the corresponding author had final responsibility for the decision to submit for publication.

Declaration of interests

MF received a research grant to Oregon Health and Science University as principal investigator for Crinetics, Chiasma, Ionis, Novartis, and Recordati and served as an occasional scientific consultant or advisory board member for Crinetics, Chiasma, Ionis, Ipsen, Novartis, Pfizer, and Recordati. AD, IB, NL, YEP, and YGP received funding to the institution as an investigator in this study from Chiasma. GV has received funding as a coinvestigator from Chiasma and Novo Nordisk; as a principal investigator from Novo Nordisk and Camurus; and has received speaker honoraria from Novo Nordisk, Eli Lilly, Servier, Pfizer, Ipsen, Novartis, AstraZeneca, and Boehringer Ingelheim. DM received funding to institution and team as a principal investigator for a clinical study from Chiasma. MEM received research grants to institution from Chiasma, Novartis, Ionis, and Crinetics; and received consulting fees from Chiasma and Novartis. GR received funding as a research investigator for Chiasma, Pfizer, and Novartis; speaker honoraria from Ipsen, Novartis, Pfizer, and Recordati Rare Diseases; consulting fees from Pfizer, Recordati Rare Diseases, and Ipsen; and has served as an advisory board member for Pfizer and Recordati Rare Diseases. EG received speaker honoraria and support for attending meetings from Pfizer and Ipsen, and payment for expert testimony from Pfizer. YG-S, GP, and AH are employees of Chiasma. WHL was a previous employee of Chiasma and is a current

employee of Recordati Rare Diseases. MBG received research support from Chiasma, Corcept, Crinetics, Ipsen, Novartis, Opico, Pfizer, Strongbridge, and Teva; support for attending meetings or travel from Chiasma; and consulting fees from Novo Nordisk. NRB declares no competing interests. SM has received consulting fees for Ionis, Mediatech, Crinetics, Rami, and Chiasma; grant funding from Pfizer; funding as a research investigator for Ipsen; and has served as an advisory board member for Chiasma. CJS has received consultancy fees and speaker honoraria from Chiasma, Pfizer, Ipsen, Sandoz-Hexal, Novo-Nordisk, and Crinetics, and served as an advisory board member for Chiasma.

Data sharing

The datasets generated or analysed in this trial are not publicly available but are available from the corresponding author on reasonable request.

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