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Clinical Research Article

MPOWERED Trial Open-Label Extension: Long-term Efficacy and Safety Data for Oral Octreotide Capsules in Acromegaly

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Abstract

Context: The MPOWERED core trial (NCT02685709) and open-label extension (OLE) phase investigated long-term efficacy and safety of oral octreotide capsules (OOC) in patients with acromegaly. Core trial primary endpoint data demonstrated noninferiority to injectable somatostatin receptor ligands (iSRLs). Core trial completers were invited to participate in the OLE phase.

Objective: To assess long-term efficacy and safety of OOC in patients with acromegaly who previously responded to and tolerated both OOC and injectable octreotide/lanreotide and completed the core phase.

Methods: The unique study design of transitioning between OOC and iSRLs allowed within-patient evaluations. The proportion of biochemical responders (insulin-like growth factor I < 1.3 × upper limit of normal) at end of each extension year who entered that year as responders was the main outcome measure.

Results: At year 1 extension end, 52/58 patients from both the monotherapy and the combination therapy groups were responders (89.7%; 95% CI 78.8-96.1), 36/41 (87.8%; 95% CI 73.8-95.9) in year 2, and 29/31 (93.5%; 95% CI 78.6-99.2) in year 3. No new or unexpected safety signals were detected; 1 patient withdrew owing to treatment failure. Patients who transitioned from iSRLs in the core trial to OOC in the OLE phase reported improved treatment convenience/satisfaction and symptom control.

Conclusion: Patient-reported outcome data support for the first time that transitioning patients randomized to iSRL (who previously responded to both OOC and iSRLs) back to OOC had a significant effect on patients' symptoms score in a prospective cohort. The MPOWERED OLE showed long-term maintenance of response and sustained safety with OOC.

Key Words: somatostatin, acromegaly, IGF-I, growth hormone excess/acromegaly, clinical trials

Abbreviations: Acro-TSQ, Acromegaly Treatment Satisfaction Questionnaire; AE, adverse event; IGF, insulin-like growth factor; iSRL, injectable somatostatin receptor ligand; LOCF, last observation carried forward; OOC, oral octreotide capsules; OLE, open-label extension; PRO, patient-reported outcome; QOL, quality of life; RCT, randomized controlled treatment; SAE, serious adverse event; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

The MPOWERED (**M**aintenance of acromegaly **P**atients with **O**ctreotide capsules compared **W**ith injections—**E**valuation of **RE**sponse **D**urability; NCT02685709) phase 3 trial was the first head to head evaluation of injectable somatostatin receptor ligands (iSRLs) and oral octreotide capsules (OOC) (1). The core study demonstrated that OOC had a consistent safety profile with that of iSRLs and that OOC were noninferior; response to OOC was maintained in 91% of patients, and response to iSRLs was maintained in 100%, achieving the noninferiority criterion of −20% (2). After completing the MPOWERED core study, patients were invited to enroll in an open-label extension (OLE) phase to receive OOC

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regardless of randomized controlled treatment (RCT) assignment (3). The trial and its OLE encompassed a design to have patients transition between iSRLs to OOC, providing multiple opportunities to explore outcomes on each agent within the same patient (Fig. 1).

The objective of the OLE phase of the MPOWERED trial was to assess long-term efficacy, safety, and patient-reported outcomes (PROs) of OOC in patients with acromegaly who had previously responded to and tolerated both oral octreotide and octreotide or lanreotide iSRLs and completed the core phase of MPOWERED per protocol.

Materials and Methods

Study Design and Participants

MPOWERED (NCT02685709) (1) was a global, phase 3, randomized, open-label, active-controlled, multicenter trial that enrolled participants from 29 clinical sites in Austria, France, Germany, Hungary, Italy, Lithuania, Russia, Serbia, Spain, and the United States. The core study started on February 11, 2016, and the OLE phase continued until August 27, 2021.

Eligibility criteria for the Run-in and RCT phases were previously published. Patients were eligible to enroll in the OLE phase and receive OOC for ≤5 years or until product marketing or termination by the sponsor if they completed the core trial, consisting of screening, Run-in, and RCT phases, in either arm or as part of the combination phase substudy of OOC and cabergoline (2). Other eligibility criteria included insulin-like growth factor I (IGF-I) level <1.3 times the upper limit of normal (ULN), OOC not being commercially available in the patient's region or country, patient not currently having study medication withheld due to a study medication–related adverse event (AE), and patient not having any clinically significant or unstable medical or surgical condition detected or worsened during the study that would preclude safe participation and completion of the OLE phase. Written informed consent was provided by all patients before initiating any aspect of the study. An additional consent form was signed by all patients to continue in the OLE phase. 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 institutional review board (local or central) or independent ethics committee reviewed and approved the protocol prior to study initiation, and a steering committee and an independent data monitoring committee provided study oversight.

Procedures

OOC (MYCAPSSA®, Amryt Pharma; Dublin, Ireland) were given twice a day on an empty stomach with a glass of water (ie, ≥1 hour before a meal or ≥2 hours after a meal) (2). Patients receiving OOC during the RCT phase or combination substudy continued with their current OOC regimen when entering the OLE phase. Those receiving iSRLs in the RCT phase began receiving their effective dose without any titration when entering the OLE phase. The effective dose was determined during the Run-in phase for all patients, as described previously (2).

IDS-iSYS IGF-I (IS-3900; Immunodiagnostic Systems) was used to measure IGF-I concentrations (2). IGF-I was assessed in months 3 and 6 after entering the OLE phase and then every 6 months.

Active symptoms of acromegaly were assessed in months 3, 6, 9, and 12 followed by every 6 months per consensus guidelines designating acromegaly symptoms as a core clinical outcome in prospective trials evaluating new treatments (2). Symptoms were assessed by acromegaly directed physical examination, as outlined previously (2).

Participants completed the Acromegaly Treatment Satisfaction Questionnaire (Acro-TSQ), a validated PRO tool used to assess overall treatment satisfaction and convenience and patient perception of adverse drug reactions and symptomatic control, on months 3, 6, and 12 followed by every 12 months during the OLE phase (2-4).

Description of Populations Analyzed

The extension analysis set (EXT-AS) is defined as all patients who were enrolled into the study extension phase. This population was used for analysis of the efficacy and safety data during the OLE phase. Data are also presented for the patient populations who received OOC (n = 35) or iSRLs during the RCT phase (n = 19), and all patients who completed the RCT phase as responders (defined as IGF-I < 1.3 × ULN).

Outcomes

The primary efficacy endpoint was the proportion of patients who were biochemical responders at the end of each year of the extension out of those who entered that year as responders. A patient was considered a responder at the beginning or end of the year if their IGF-I was <1.3 × ULN. Responder status of the participants for the first, second, and third year was determined based on the baseline value, week 48 value, and week 96 value during the OLE phase, respectively. This was assessed using nonresponse imputation (early discontinuations were considered nonresponders). Post hoc exploratory assessment of the primary endpoint included results using last observation carried forward (LOCF) imputation in all patients (including those who entered the combination substudy) and in patients who received OOC monotherapy (RCT phase completers).

Secondary endpoints included the proportion of patients who completed each year of the OLE phase and the change in IGF-I from baseline of the OLE phase to the end of treatment for each year of the OLE phase. Key exploratory endpoints included PROs assessed through domain scores of the Acro-TSQ, item-level analysis of symptom control from the Acro-TSQ, and total number and type of active acromegaly symptoms.

Safety variables and assessments included, but were not limited to, the frequency and severity of treatment-emergent adverse events (TEAEs; defined as an AE with an onset on or after study drug initiation for the OLE phase) and serious adverse events (SAEs), as well as clinically significant laboratory abnormalities, vital sign abnormalities, and 12-lead electrocardiograms.

Statistical Analysis

Data collected in the study extension phase are summarized by time point using descriptive statistics. Analyses are based on the EXT-AS. Unless stated otherwise, missing data were maintained as missing. For continuous variables, descriptive

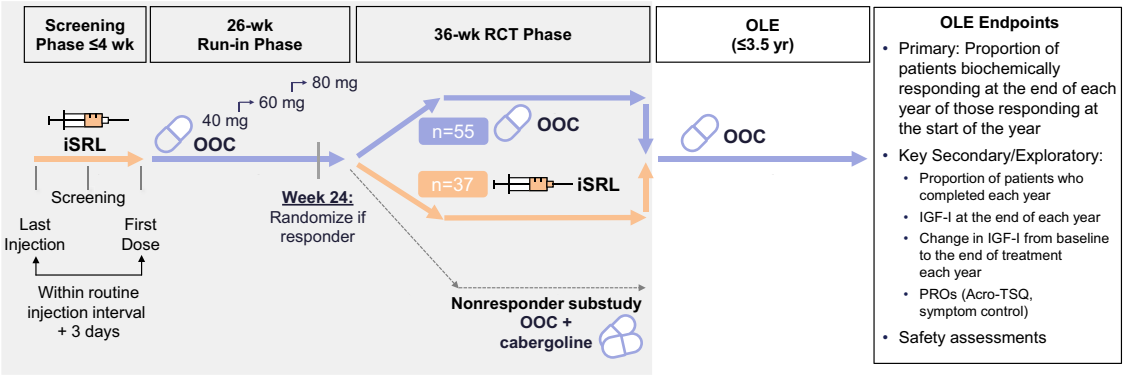

Figure 1. Study design of MPOWERED core study and OLE phase. Abbreviations: Acro-TSQ, Acromegaly Treatment Satisfaction Questionnaire; IGF-I, insulin-like growth factor I; iSRL, injectable somatostatin receptor ligand; OLE, open-label extension; OOC, oral octreotide capsule; PRO, patient-reported outcome; RCT, randomized controlled treatment.

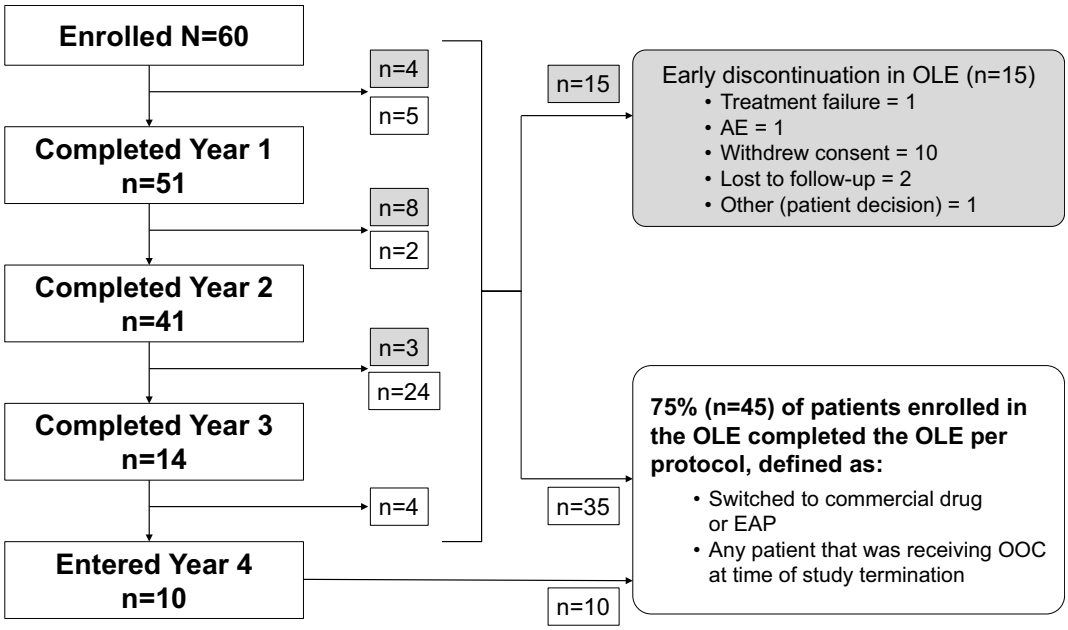

Figure 2. Patient disposition during OLE phase. Abbreviations: AE, adverse event; EAP, expanded access program; OLE, open-label extension; OOC, oral octreotide capsule.

statistics included number of participants (n), mean (SD), median, 25th percentile, 75th percentile, minimum, and maximum.

For the primary efficacy endpoint, if a patient was missing the end of study extension year assessment, the last value during that year was used to impute the end of year value (LOCF approach).

Results

Of 60 patients enrolled in the OLE phase, 35 (58.3%) received OOC in the RCT phase, 19 (31.7%) received iSRLs, and 6 (10%) were in the combination substudy. Over the entire course of the OLE phase, 45 of 60 patients (75%) completed the OLE phase per protocol, defined by having completed the relevant treatment period, having switched to commercial drug or expanded access program, or having been on OOC at the time of study termination. Fifty-six of 60 patients (93.3%) completed year 1 per protocol, 43/47 (91.5%) completed year 2, and 34/37 (91.9%) completed year 3. Fifteen patients discontinued during the OLE phase. Causes of discontinuation included AEs in some, but not all, patients: n = 1 (did not early terminate the OLE phase but was listed as such owing to a temporary interruption of the study drug due to TEAEs that were deemed unrelated to study drug); n = 10, withdrawal by patient; n = 1, treatment failure (IGF-I ≥ 1.3 × ULN); n = 2, lost to follow-up; n = 1, other (recorded as "patient decision" by investigator, rather than the option of "withdrawal by patient"). Ten patients withdrew themselves from the OLE phase: 8 patients were willing to revert to iSRLs, 2 patients for unknown reasons (Fig. 2). The OLE phase included 17 patients (28.3%) who identify as male and 43 patients (71.7%) who identify as female. Additional demographic and acromegaly baseline characteristics can be found in Table 1.

For the primary efficacy endpoint, nonresponse imputation was completed assessing all patients who entered the OLE

Table 1. Table of demographic and acromegaly baseline[a] of OLE phase characteristics

Characteristic	OOC in RCT Phase (n = 35)	iSRL in RCT Phase (n = 19)	Combination substudy (n = 6)	Total (N = 60)
Age at screening[b], year, mean (SD)	52.5 (10.82)	54.4 (9.05)	61.5 (5.96)	54.0 (10.13)
Sex, n (%)				
Male	11 (31.4)	5 (26.3)	1 (16.7)	17 (28.3)
Female	24 (68.6)	14 (73.7)	5 (83.3)	43 (71.7)
Race, n (%)				
Black/African or African American	2 (5.7)	0	0	2 (3.3)
White	32 (91.4)	18 (94.7)	6 (100)	56 (93.3)
Other	1 (2.9)	1 (5.3)	0	2 (3.3)
Ethnicity				
Hispanic or Latino	1 (2.9)	1 (5.3)	0	2 (3.3)
Not Hispanic or Latino	33 (94.3)	17 (89.5)	6 (100)	56 (93.3)
Not reported	1 (2.9)	1 (5.3)	0	2 (3.3)
BMI at screening, kg/m^2, mean (SD)	27.7 (3.96)	27.8 (3.86)	32.5 (5.97)	28.2 (4.31)
Duration of acromegaly, n (%)				
<10 year	10 (28.6)	12 (63.2)	2 (33.3)	24 (40.0)
10–<20 year	20 (57.1)	4 (21.1)	3 (50.0)	27 (45.0)
≥ 20 year	5 (14.3)	3 (15.8)	1 (16.7)	9 (15.0)
Pituitary tumor type[c], n (%)				
Microadenoma	4 (11.4)	5 (26.3)	2 (33.3)	11 (18.3)
Macroadenoma	30 (85.7)	14 (73.7)	4 (66.7)	48 (80.0)
Other	1 (2.9)	0	0	1 (1.7)
Residual tumor size, n (%)				
No remnants	19 (54.3)	12 (63.2)	2 (33.3)	33 (55.0)
<5 mm	4 (11.4)	3 (15.8)	1 (16.7)	8 (13.3)
5-10 mm	7 (20.0)	3 (15.8)	2 (33.3)	12 (20.0)
>10 mm	5 (14.3)	1 (5.3)	1 (16.7)	7 (11.7)
Previous acromegaly treatments, n (%)				
Surgery only	25 (71.4)	12 (63.2)	4 (66.7)	41 (68.3)
Radiotherapy only	1 (2.9)	0	0	1 (1.7)
Surgery and radiotherapy	6 (17.1)	4 (21.1)	1 (16.7)	11 (18.3)
Neither surgery nor radiotherapy	3 (8.6)	3 (15.8)	1 (16.7)	7 (11.7)
Extension Baseline IGF-I, n (%)				
≤1 × ULN	24 (68.6)	16 (84.2)	2 (33.3)	42 (70.0)
>1 to <1.3 × ULN	10 (28.6)	3 (15.8)	4 (66.7)	17 (28.3)
≥1.3 × ULN	1 (2.9)	0	0	1 (1.7)
Previous iSRL treatment, n (%)				
Low	9 (25.7)	4 (21.1)	1 (16.7)	14 (23.3)
Middle	13 (37.1)	9 (47.4)	1 (16.7)	23 (38.3)
High	13 (37.1)	6 (31.6)	4 (66.7)	23 (38.3)
Active symptoms, n (%)				
0	7 (20.0)	4 (21.1)	0	11 (18.3)
≥1	28 (80.0)	15 (78.9)	6 (100)	49 (81.7)
≥2	22 (62.9)	14 (73.7)	6 (100)	42 (70.0)
≥3	13 (37.1)	11 (57.9)	4 (66.7)	28 (46.7)

Abbreviations: BMI, body mass index; iSRL, injectable somatostatin receptor ligand, IGF-I, insulin-like growth factor I; IQR, interquartile range; OOC, oral octreotide capsules; RCT, randomized controlled treatment; ULN, upper limit of normal.

[a]Baseline for the extension phase was the last value recorded prior to or equal to the earliest date between the date of informed consent for the Extension phase and the date of the first dose of treatment in the extension phase.

[b]Age (year) = year of screening visit – year of birth.

[c]Microadenoma was defined as tumor size ≤10 mm, macroadenoma was defined as tumor size >10 mm, undetermined and not visible were defined as "other."

Table 2. Primary results

Primary endpoint:	
Proportion of patients who were biochemical responders at the end of each year of the OLE phase out of those who entered that year as responders; n/N, Z% (95% CI)	
LOCF[a]	Year 1: 52/58, 89.7% (95% CI 78.8-96.1)
	Year 2: 36/41, 87.8% (95% CI 73.8-95.9)
	Year 3: 29/31, 93.5% (95% CI 78.6-99.2)
LOCF RCT phase completers	Year 1: 49/52, 94.2%, (95% CI 84.1-98.8)
	Year 2: 34/38, 89.5% (95% CI 75.2-97.1)
	Year 3: 27/29, 93.1% (95% CI 77.2-99.2)
Nonresponse imputation[b]	Year 1: 50/58, 86.2% (95% CI 74.6-93.9)
	Year 2: 34/42, 81.0% (95% CI 65.9-91.4)
	Year 3: 27/31, 87.1% (95% CI 70.2-96.4)

Abbreviations: LOCF, last observation carried forward; OLE, open-label extension; RCT, randomized controlled treatment.
[a]Only patients who entered a year as responders and also had end of year response were included in that year's analysis. LOCF approach was used to impute the end of year values for patients who early terminated the extension phase.
[b]Subjects that terminated early during a given year were characterized as non-responders. If a subject was missing the end of study extension year assessment without discontinuation, then the last value during that year was used to impute the end of year value.

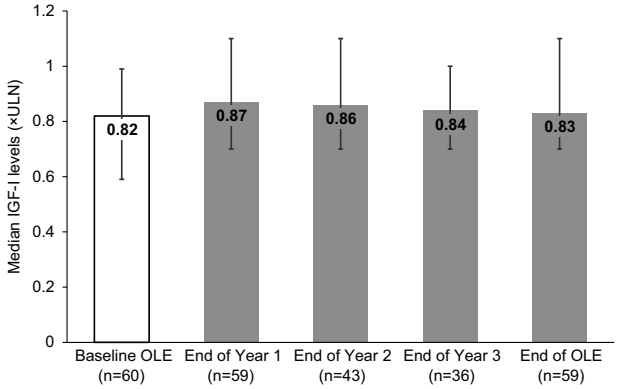

Figure 3. Median IGF-I levels at end of each year in OLE phase. Error bars denote interquartile ranges. Abbreviations: IGF-I, insulin-like growth factor I; OLE, open-label extension; ULN, upper limit of normal.

phase (both those completing the RCT phase on OOC monotherapy as well as those completing the combination phase substudy). This analysis showed that at the end of year 1 of the OLE phase, 50 out of 58 patients (86.2%; 95% CI 74.6-93.9) were responders, 34 out of 42 patients (81.0%; 95% CI 65.9-91.4) were responders at the end of the second year, and 27 out of 31 (87.1%; 95% CI 70.2-96.4) were responders at the end of the third year. A post hoc exploratory analysis of this same primary endpoint population was performed using LOCF imputation. Among patients who were responders at the start of each year assessed in the OLE phase, 52 out of 58 patients (89.7%; 95% CI 78.8-96.1) were responders at the end of the first year of OLE phase, 36/41 (87.8%; 95%, CI 73.8-95.9) were responders at the end of year 2, and 29/31 (93.5%; 95% CI 78.6-99.2) were responders at the end of year 3 (Table 2). Results for patients who finished the RCT phase as completers (OOC monotherapy, did not enter the combination substudy) are also presented in Table 2. The mean IGF-I change from baseline of the OLE phase to the end of the first year of the OLE phase was 0.06 × ULN (SD 0.235; IQR 0.0-0.2) using LOCF. The mean IGF-I change from baseline to the end of years 2 and 3 was 0.11 × ULN (SD 0.302; IQR −0.1 to 0.4), and 0.07 × ULN (SD 0.315; IQR −0.1 to 0.2), respectively. Median IGF-I levels at the end of each year of the OLE phase were maintained within normal limits and are reported in Fig. 3.

Item-level analysis of the Acro-TSQ symptom control responses revealed that there was a 66.5% increase in patients transitioning from iSRLs in the RCT phase to OOC during the OLE phase who reported "Excellent" or "Very good" symptom control (31.6% and 47.4%, respectively) at the end of OLE phase (Fig. 4). This PRO was also supported by measurement of total active symptoms (Table S1 and Fig. S1 (5)).

Patients who were treated with iSRLs in the RCT phase and transitioned to OOC in the OLE phase also reported a reduction in breakthrough symptoms. These patients also showed improvements in the Treatment Convenience and Treatment Satisfaction domain scores on the Acro-TSQ, while patients who were treated with OOC during the RCT phase maintained their Acro-TSQ scores during the OLE phase (Fig. 5). At the end of the OLE phase, the majority of patients expressed a preference for OOC taken twice daily (Fig. S2 (5)).

The overall median exposure to OOC was 2.2 years or 114.43 weeks (range 9.1-181 weeks). Mean compliance rate for OOC was 97.1% (median 99%). During the OLE phase, 32/60 patients (53.3%) experienced ≥1 TEAE, 12 (20%) experienced ≥1 TEAE that was considered related to study drug, 8 (13.3%) experienced ≥1 severe TEAE, and 2 (3.3%) were withdrawn from the study due to a TEAE (pneumonia viral and cholecystitis acute). TEAEs were mostly gastrointestinal and mild to moderate in intensity, and the most common TEAEs were diarrhea (6 patients, 10.0%), nasopharyngitis (5 patients, 8.3%), and nausea (4 patients, 6.7%) (Table 3). The only TEAE deemed treatment related and reported in ≥5% of patients was diarrhea (5.0%). Gastrointestinal AEs were most commonly reported during the 12 months of the OLE phase: 8 patients (13.3%) experienced an event during the first 6 months, and 5 patients (8.3%) experienced an event during month 6 to month 12. Incidence and periodicity of gastrointestinal TEAEs during the OLE phase were similar between patients randomized to either OOC or iSRLs in the RCT phase of MPOWERED. Five patients (8.3%) experienced a total of 8 SAEs; 1 of which was deemed related to study drug (cholecystitis acute). Other SAEs deemed unrelated to study drug included gastrointestinal disorders (hiatus hernia, n = 1; vomiting, n = 2; pancreatitis chronic, n = 1), metabolism and nutrition disorders (lactic acidosis, n = 1), neoplasms (clear cell renal carcinoma, n = 1), and infections and infestations (pneumonia viral, n = 1). Overall, no clinically meaningful changes were observed in vital signs or laboratory safety parameters, including glycemic control and liver function tests. Concomitant medication use for diabetes during the OLE phase was limited to very few patients, and there were no observed changes from baseline to the end of the extension. No deaths occurred during the OLE phase. A post hoc analysis of patients who received iSRLs during the RCT phase and transitioned to >40 mg of OOC in the OLE phase demonstrated that there were no safety issues identified with restarting OOC at >40 mg.

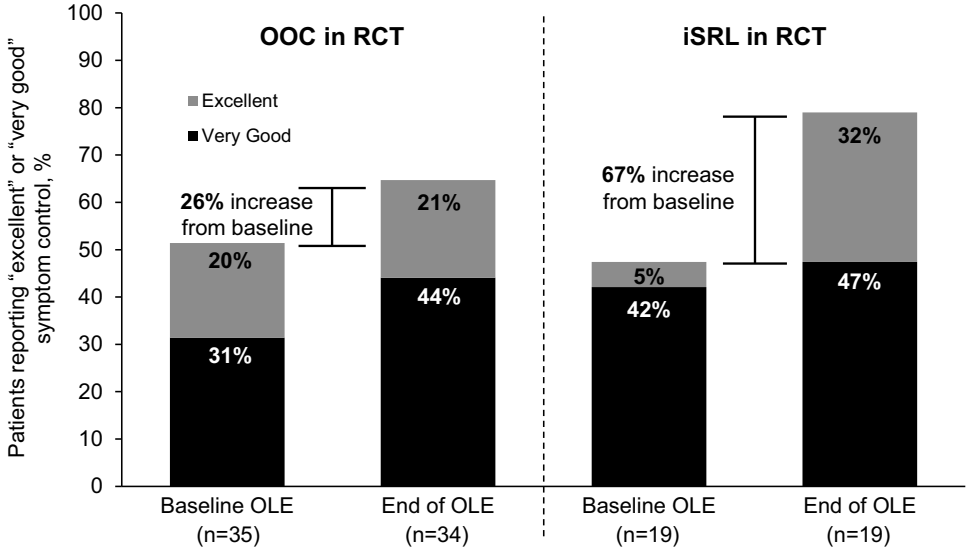

Figure 4. Change in reported symptom control from baseline to end of OLE phase as measured by the Acro-TSQ. End of OLE was defined as completing extension per protocol (<3.5 years), using LOCF. Abbreviations: Acro-TSQ, Acromegaly Treatment Satisfaction Questionnaire; iSRL, injectable somatostatin receptor ligand; LOCF, last observation carried forward; OLE, open-label extension; OOC, oral octreotide capsules; RCT, randomized controlled treatment.

Discussion

Acromegaly is a rare disease with enormous treatment burden, and patients often receive delayed diagnoses; therefore, surgery may not be sufficient or appropriate, and long-term medical therapy may be required (6-16). Several treatment options are widely available with different mechanisms and mode of administration, allowing for individualized treatment based on tumor characteristics, biochemical values, and patient preference (6, 9). The MPOWERED study was the first head to head evaluation of OOC with iSRLs (2). The results presented from the OLE phase of the MPOWERED study highlight the overall maintenance of biochemical response using OOC in a large population responding to and tolerating both OOC and iSRLs as well as new supporting data on PROs. These results were consistent with the results of the core study, with the addition of long-term safety of OOC throughout the OLE phase (2). The trial was designed to provide important data, as patients transitioned between administration methods multiple times, with all patients receiving OOC during the Run-in phase, some of the patients randomized to iSRLs during the RCT phase, and all patients returning to OOC during the OLE phase.

Patients with acromegaly experience a high treatment burden due to iSRL treatment, highlighting the need for an oral option (10, 12-15, 17). Throughout the core study and OLE phase, patients with previous exposure to iSRLs transitioned to oral administration during designated phases owing to study design (2). Here we show improvement in measures of PROs while on OOC in patients who responded to and tolerated both treatments.

PROs are becoming increasingly important in clinical studies, specifically those performed in patients with acromegaly (6, 18-22). The improvement of scores on the Acro-TSQ and relevant PROs observed in this study and others in patients receiving treatment for acromegaly highlight the important correlation between appropriate management of both disease and acromegaly symptoms and the improvement in quality of life (QoL) (2, 6, 23-25). A study of long-term QoL comparing postsurgery patients with acromegaly with or without the requirement of additional medication to maintain biochemical control found that patients who required medication showed improvement in QoL over time (24). Another study evaluating multiple aspects of QoL in patients with acromegaly found that when comparing patients receiving treatment for acromegaly, patients who maintained disease control scored higher on the Acromegaly Quality of Life Questionnaire, another common PRO used in acromegaly (25). Maintenance of disease control, symptoms, side effects, and related complications are of the utmost importance, as all can impact QoL (4, 6, 9, 18, 23, 26, 27). Additionally, at the end of the extension phase, most patients indicated their preference for OOC taken twice daily, a sentiment that was supported by reports of increased anxiety and frustration in patients receiving iSRLs compared with patients receiving OOC, emphasizing the positive impact OOC could have on QoL (28, 29).

The OLE phase of the MPOWERED study was the largest long-term follow-up for OOC and demonstrated a high percentage of patients maintaining biochemical response while receiving OOC monotherapy with a favorable long-term safety profile of OOC (30). Forty-five of 60 patients completed the OLE phase per protocol; the patient population decreased each year as patients completed the relevant treatment period while still responding to OOC or switched to commercial drug once available or expanded access program. Importantly, treatment failure occurred in only 1 patient. Patients were exposed to OOC for ≤181 weeks, and response was maintained throughout without effects often experienced by patients with acromegaly receiving iSRLs, including injection site reactions or breakthrough symptoms that are commonly observed toward the end of the injection interval, consistent with the upward trend of IGF-I levels from the midpoint to the timepoint just before the next injection seen in these patients (11-14, 31-33). Those who transitioned from iSRLs in the RCT phase to OOC in the OLE phase demonstrated improvements in symptom control, treatment convenience, and treatment satisfaction.

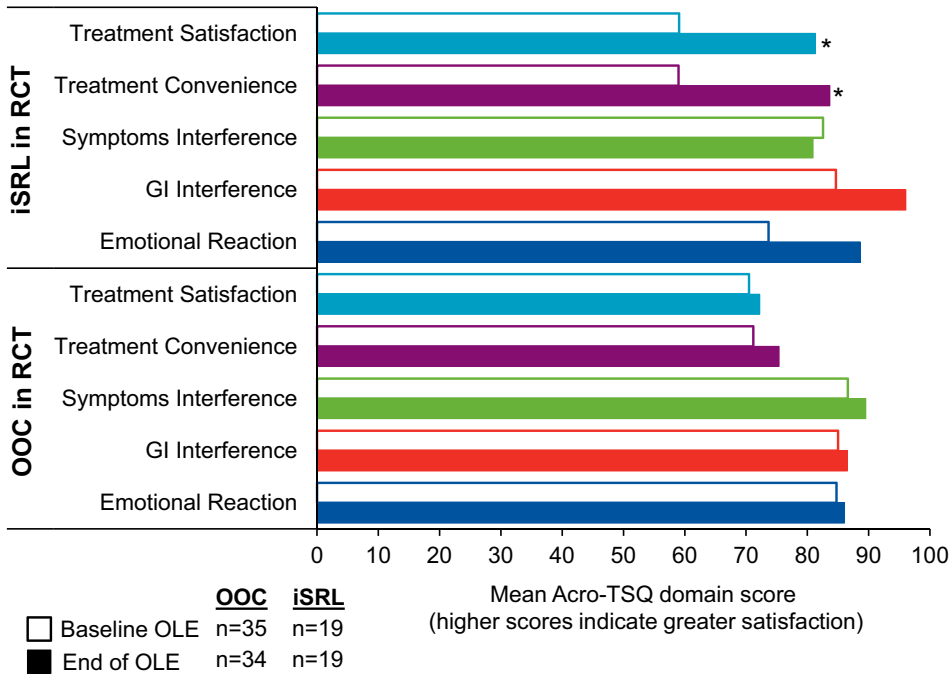

Figure 5. Overall effect in Acro-TSQ domains in OLE phase. End of OLE was defined as completing extension per protocol (<3.5 years), using LOCF. *Statistically significant change. Exploratory analysis only; the OLE phase of MPOWERED was not powered for statistical testing. Treatment satisfaction measures satisfaction with current treatment. Treatment convenience measures convenience of current treatment, if it is easy or difficult to have the treatment administered exactly as prescribed, and if it impacts the patient's ability to make plans. GI interference measures how much GI side effects have interfered with the patient's ability to do daily activities (eg, walking or moving about, going up/down stairs, household chores, errands, cooking, taking care of children or grandchildren, etc.), participate in leisure activities (eg, going to restaurants or movies, watching sports, exercising, spending time with friends and family, etc.), or to be productive at work. Symptoms interference measures how much acromegaly symptoms have interfered with the previously mentioned activities. Emotional reaction measures to what degree patients feel certain emotions when thinking about or receiving their acromegaly treatment. Abbreviations: Acro-TSQ, Acromegaly Treatment Satisfaction Questionnaire; GI, gastrointestinal; iSRL, injectable somatostatin receptor ligand; OLE, open-label extension; OOC, oral octreotide capsules; RCT, randomized controlled treatment.

Table 3. Most common TEAEs (≥5%) in OLE phase

	Overall (N = 60)
Patients with ≥1 TEAE	32 (53.3)
Gastrointestinal disorders	17 (28.3)
Diarrhea	6 (10.0)
Nausea	4 (6.7)
Abdominal pain upper	3 (5.0)
Vomiting	3 (5.0)
Infections and infestations	10 (16.7)
Nasopharyngitis	5 (8.3)
Musculoskeletal and connective tissue disorders	10 (16.7)
Arthralgia	3 (5.0)
Arthritis	3 (5.0)
Back pain	3 (5.0)
Investigations	7 (11.7)
Blood pressure increased	3 (5.0)

Abbreviations: OLE, open-label extension; TEAE, treatment-emergent adverse event.
A TEAE was defined as an adverse event with an onset on or after study drug initiation for the Extension phase (Day 0). Adverse events were coded using the *Medical Dictionary for Regulatory Activities* Version 18.1.

Another finding of clinical importance is that no new safety issues were observed with patients who received iSRLs in the RCT phase and initiated OOC at doses >40 mg/day in the OLE phase, which is higher than the current recommended initiation dose. However, it is important to note that the population included in the MPOWERED OLE phase had already demonstrated tolerability of OOC during the Run-in phase, and it is therefore subject to selection bias. The biochemical efficacy and safety results from the OLE phase also are consistent with previous data (32, 34).

There are several limitations of the OLE phase as well as the analysis, including selection bias. Of note, patients who enrolled in the core study did so with the intention of possibly receiving OOC. Patients also elected to continue into the OLE phase in order to either receive OOC after being randomized to iSRLs in the RCT phase, as there was no control group included in the OLE phase and all patients received OOC, or because they were randomized to OOC in the RCT phase and were benefitting from treatment. Though less likely to be relevant for the majority of patients, the lack of a control group in the OLE phase of the trial prevented assessment of active disease.

In conclusion, the study allowed for long-term novel assessment of biochemical efficacy, safety, and PROs in patients who transitioned multiple times between iSRLs and OOC and confirmed the clinical benefit of OOC. Results from the OLE phase of the MPOWERED study further support the effective long-term use and the known safety profile of OOC in patients with acromegaly.

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Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. Supplementary materials are available at: https://doi.org/10.6084/m9.figshare.22666633.

Clinical Trial Information

NCT02685709 (registered February 14, 2016).

References

1. ClinicalTrials.gov. Comparison of oral octreotide capsules to injectable somatostatin analogs in acromegaly (MPOWERED). NCT02685709. February 19, 2016. Updated April 22, 2022. Accessed October 13, 2022. https://clinicaltrials.gov/ct2/show/NCT02685709
2. Fleseriu M, Dreval A, Bondar I, *et al.* Maintenance of response to oral octreotide compared with injectable somatostatin receptor ligands in patients with acromegaly: a phase 3, multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol*. 2022;10(2):102-111.
3. Fleseriu M, Fogelfeld L, Gordon MB, *et al.* An evaluation of the Acromegaly Treatment Satisfaction Questionnaire (Acro-TSQ) in adult patients with acromegaly, including correlations with other patient-reported outcome measures: data from two large multicenter international studies. *Pituitary*. 2020;23(4):347-358.
4. Fleseriu M, Molitch M, Dreval A, *et al.* Disease and treatment-related burden in patients with acromegaly who are biochemically controlled on injectable somatostatin receptor ligands. *Front Endocrinol (Lausanne)*. 2021;12:627711.
5. Fleseriu M, Molitch M, Dreval A, *et al.* Supplemental Material for "MPOWERED trial open-label extension: long-term efficacy and safety data for oral octreotide capsules in acromegaly." Figshare. Deposited April 20, 2023. https://doi.org/10.6084/m9.figshare.22666633
6. Fleseriu M, Langlois F, Lim DST, Varlamov EV, Melmed S. Acromegaly: pathogenesis, diagnosis, and management. *Lancet Diabetes Endocrinol*. 2022;10(11):804-826.
7. Melmed S. Pituitary-tumor endocrinopathies. *N Engl J Med*. 2020;382(10):937-950.
8. Melmed S, Kaiser UB, Lopes MB, *et al.* Clinical biology of the pituitary adenoma. *Endocr Rev*. 2022;43(6):1003-1037.
9. Sherlock M, Woods C, Sheppard MC. Medical therapy in acromegaly. *Nat Rev Endocrinol*. 2011;7(5):291-300.
10. Biermasz NR. The burden of disease for pituitary patients. *Best Pract Res Clin Endocrinol Metab*. 2019;33(2):101309.
11. Geer EB, Sisco J, Adelman DT, *et al.* Observed discordance between outcomes reported by acromegaly patients and their treating endocrinology medical provider. *Pituitary*. 2020;23(2):140-148.
12. Liu S, Adelman DT, Xu Y, *et al.* Patient-centered assessment on disease burden, quality of life, and treatment satisfaction associated with acromegaly. *J Investig Med*. 2018;66(3):653-660.
13. Strasburger CJ, Karavitaki N, Störmann S, *et al.* Patient-reported outcomes of parenteral somatostatin analogue injections in 195 patients with acromegaly. *Eur J Endocrinol*. 2016;174(3):355-362.
14. Yedinak C, Pulaski Liebert KJ, Adelman DT, Williams J. Acromegaly: current therapies benefits and burdens. *Clin Pract*. 2018;15(2):499-511.
15. Webb SM, Crespo I, Santos A, Resmini E, Aulinas A, Valassi E. Management of endocrine disease: quality of life tools for the management of pituitary disease. *Eur J Endocrinol*. 2017;177(1):R13-r26.
16. Katznelson L, Laws ER, Jr., Melmed S, *et al.* Acromegaly: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;99(11):3933-3951.
17. Geer EB, Sisco J, Adelman DT, *et al.* Patient reported outcome data from acromegaly patients treated with injectable somatostatin receptor ligands (SRLs) in routine clinical practice. *BMC Endocr Disord*. 2020;20(1):117.
18. Cangiano B, Giusti E, Premoli C, *et al.* Psychological complications in patients with acromegaly: relationships with sex, arthropathy, and quality of life. *Endocrine*. 2022;77(3):510-518.
19. Kyte DG, Draper H, Ives J, Liles C, Gheorghe A, Calvert M. Patient reported outcomes (PROs) in clinical trials: is 'in-trial' guidance lacking? a systematic review. *PLoS One*. 2013;8(4):e60684.
20. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas*. 2018;9:353-367.
21. Rivera SC, Kyte DG, Aiyegbusi OL, Slade AL, McMullan C, Calvert MJ. The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis. *Health Qual Life Outcomes*. 2019;17(1):156.
22. Giustina A, Barkan A, Beckers A, *et al.* A consensus on the diagnosis and treatment of acromegaly comorbidities: an update. *J Clin Endocrinol Metab*. 2020;105(4):dgz096.
23. Fleseriu M, Biller BMK, Freda PU, *et al.* A Pituitary Society update to acromegaly management guidelines. *Pituitary*. 2021;24(1):1-13.
24. Kimball A, Dichtel LE, Yuen KCJ, *et al.* Quality of life after long-term biochemical control of acromegaly. *Pituitary*. 2022;25(3):531-539.
25. Pivonello R, Auriemma RS, Delli Veneri A, *et al.* Global psychological assessment with evaluation of life and sleep quality, sexual and cognitive function in a large number of patients with acromegaly: a cross-sectional study. *Eur J Endocrinol*. 2022;187(6):823-845.
26. Colao A, Bronstein MD, Brue T, *et al.* Pasireotide for acromegaly: long-term outcomes from an extension to the phase III PAOLA study. *Eur J Endocrinol*. 2020;182(6):583.

27. Giustina A, Barkhoudarian G, Beckers A, *et al.* Multidisciplinary management of acromegaly: a consensus. *Rev Endocr Metab Disord*. 2020;21(4):667-678.
28. Gadelha MR, Wildemberg LE, Kasuki L. The future of somatostatin receptor ligands in acromegaly. *J Clin Endocrinol Metab*. 2022;107(2):297-308.
29. Gordon MB, Fleseriu M, Dreval AV, *et al.* Improved acromegaly patient satisfaction with oral octreotide capsules compared with injectable somatostatin receptor ligands in the MPOWERED trial. *J Endocrin Soc*. 2021;5(Suppl 1):A520-A521.
30. Samson SL, Nachtigall LB, Fleseriu M, *et al.* Durable biochemical response and safety with oral octreotide capsules in acromegaly. *Eur J Endocrinol*. 2022;187(6):733-741.
31. Geer E, Sisco J, Adelman D, *et al.* SUN-LB077 Relationship between responses from acromegaly patients treated with a stable dose of injectable somatostatin analogues in routine clinical practice and their endocrinology health care professional regarding treatment outcomes: preliminary findings. *J Endocrin Soc*. 2019;3(Suppl 1):SUN-LB077.
32. Samson SL, Nachtigall LB, Fleseriu M, *et al.* Maintenance of acromegaly control in patients switching from injectable somatostatin receptor ligands to oral octreotide. *J Clin Endocrinol Metab*. 2020;105(10):e3785-e3797.
33. Maione L, Albrici C, Grunenwald S, *et al.* IGF-I variability over repeated measures in patients with acromegaly under long-acting somatostatin receptor ligands. *J Clin Endocrinol Metab*. 2022;107(9):e3644-e3653.
34. Melmed S, Popovic V, Bidlingmaier M, *et al.* Safety and efficacy of oral octreotide in acromegaly: results of a multicenter phase III trial. *J Clin Endocrinol Metab*. 2015;100(4):1699-1708.