Clinical Study Report Synopsis	
Drug Substance	Olaparib
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An Open-Label, Single Arm, Multicentre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum-based Chemotherapy (ORZORA)

Study dates:
First subject enrolled: 28 September 2015
Last subject last visit: not applicable (ongoing study)
The analyses presented in this report are based on a cut-off date of 17 April 2020

Phase of development: Therapeutic confirmatory (III)

International Co-ordinating Investigator:
PPD
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Sponsor's Responsible Medical Officer:
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This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

The study was conducted in 8 countries: Bulgaria, Canada, Czech Republic, Hungary, Italy, Poland, Spain and the United Kingdom (UK). Sixty-six centres were initiated to enrol up to 250 ovarian cancer patients with somatic or germline breast cancer susceptibility gene mutations (s*BRCA*m or g*BRCA*m).

Publications

Pignata S, Lewis J, Tchakov I, Robertson JD, Morris T, Jayawardene D, et al. ORZORA: Open-label phase IV trial of olaparib in patients with *BRCA*-mutated ovarian cancer. European Society of Gynaecological Oncology, 19th International Meeting, Nice, France, 24-27 October 2015. (Abstract #0933, Poster #EP08)

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective		Outcome Variable
Priority	**Description**	**Description**
Primary	• To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by Investigator-assessed progression-free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 in patients with s*BRCA*m ovarian cancer. • To assess the real-world clinical effectiveness of olaparib maintenance monotherapy by Investigator-assessed PFS according to RECIST v1.1 in patients with breast cancer susceptibility gene mutated (*BRCA*m) ovarian cancer	Time from study enrolment to disease progression (assessed according to RECIST v1.1 guidelines) or death.
Secondary	To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of: a) overall survival (OS), b) time to Investigator-assessed second progression (PFS2), or death.	a) Time to death b) Time to second progression event or death if this occurs before second progression event.

Objective		Outcome Variable
Priority	**Description**	**Description**
	To assess the real-world clinical effectiveness of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer, by assessment of a) time to first subsequent therapy or death (TFST), b) time to second subsequent therapy or death (TSST) and, c) time to olaparib discontinuation or death (TDT).	a) Time to first subsequent treatment commencement or death if this occurs before commencement of first subsequent treatment b) Time to second subsequent treatment commencement or death if this occurs before commencement of second subsequent treatment c) Time to olaparib discontinuation or death if this occurs before discontinuation of olaparib maintenance therapy.
	To assess and describe the quality of life (QoL) of patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	Functional Assessment of Cancer Therapy-Ovarian (FACT-O), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue, and ORZORA QoL Additional Items Questionnaire.
	To describe patterns of routine clinical use of olaparib, the nature and patterns of adverse events (AEs) of nausea and vomiting and their impact on QoL in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer. To describe nausea/vomiting toxicity management patterns used in routine clinical practice.	Safety summary tables, Functional Living Index- Emesis (FLIE) Questionnaire, and concomitant medication use.
Safety	To assess the safety and tolerability of olaparib maintenance monotherapy in patients with *BRCA*m ovarian cancer and patients with s*BRCA*m ovarian cancer.	AEs/serious adverse events (SAEs)/AEs of special interest (AESI)
CCI [redacted]		

Objective		Outcome Variable
Priority	**Description**	**Description**
CCI		

Objective		Outcome Variable
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CCI		
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PFS: Progression-free survival; RECIST: Response Evaluation Criteria In Solid Tumours; *BRCA*m: Breast cancer susceptibility gene mutation (mutated); s*BRCA*m: Somatic *BRCA*m; AE*:* Adverse event; OS: Overall survival; PFS2: Time to Investigator-assessed second progression; TFST: Time to first subsequent therapy or death; TSST: Time to second subsequent therapy or death; TDT: Time to olaparib discontinuation or death; QoL: Quality of Life; FACT-O: Functional Assessment of Cancer Therapy-Ovarian; FACIT: Functional Assessment of Chronic Illness Therapy; FLIE: Functional Living Index-Emesis; SAE: Serious adverse event; AESI: Adverse event of special interest; AML: Acute myeloid leukaemia; CA-125: Cancer antigen-125; ctDNA: Circulating tumour DNA; DNA: Deoxyribonucleic acid; HRR: Homologous recombination repair; HRRm^: Qualifying mutation in the tumour of any of 13 genes involved in homologous recombination repair (excluding *BRCA*1 and *BRCA*2 mutations); MDS: Myelodysplastic syndrome; PFS: Progression-free survival; PFI: Progression-free interval; GCIG: Gynaecological Cancer InterGroup; LOH: Loss-of-heterozygosity

Study design

This was a prospective, open-label, single arm, multicentre study to assess the real-world clinical effectiveness and safety of olaparib maintenance monotherapy. The study was conducted in patients with platinum sensitive relapsed (PSR) g*BRCA*m or s*BRCA*m high grade epithelial ovarian (including fallopian tube or primary peritoneal) cancer, who were in

complete response (CR) or partial response (PR) to platinum-based chemotherapy. From Protocol edition 2 onwards, *BRCA* mutation status was determined through central tumour and blood testing performed by Myriad Genetics (patients enrolled under Protocol edition 1 were enrolled based on a local test). An additional, exploratory cohort of patients with *BRCA*-independent qualifying alterations in any of 13 genes (excluding *BRCA*1 and *BRCA*2 mutations) involved in the homologous recombination repair (HRR) pathway was enrolled into the study (HRRm^ cohort). The investigational clinical trial assay developed as the Lynparza HRR Assay and now called the Foundation One CDx, from Foundation Medicine Inc. (FMI) was used for this testing.

Patients were assigned olaparib capsules p.o. 400 mg twice daily. They initiated olaparib treatment within 8 weeks after their last dose of platinum-containing chemotherapy (last dose is the day of the last infusion). All patients had clinical and objective radiological tumour assessments according to modified Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 at baseline and every 12 weeks relative to date of enrolment, until objective radiological disease progression as determined by the Investigator.

Target subject population and sample size

Eligible patients had PSR high grade epithelial ovarian cancer, primary peritoneal and/or fallopian tube cancer, who were found to carry a g*BRCA* or s*BRCA* mutation, known or suspected to be deleterious. Patients had to have completed at least 2 previous lines of platinum-based therapy (e.g. containing carboplatin or cisplatin) before entry into the study, be considered platinum sensitive, and be in PR or CR after the penultimate platinum-based chemotherapy.

Patients with unknown g*BRCA*m status or patients found to carry wild type g*BRCA* (g*BRCA*wt) disease or patients previously identified as having *BRCA*m disease based on a tumour test (with unknown g*BRCA* mutation status or with previously identified g*BRCA*wt status) were considered for screening. Patients previously diagnosed with g*BRCA*m disease were not included in this study.

No formal sample size calculation was performed for this study. A total sample size of approximately 250 patients was anticipated, driven by the need to have at least 50 patients with s*BRCA*m disease, and to help understand patterns of olaparib use in routine clinical practice with the capsule formulation, and across various subgroups. Assuming that approximately 5% of patients with *BRCA*wt disease screened in the study carried a qualifying genetic alteration in any of the 13 genes involved in the HRR pathway (excluding *BRCA*1 and *BRCA*2 mutations), approximately 25 patients were to be included in the HRRm^ cohort.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Olaparib 400 mg bid (50 mg capsules; orally administered).

Duration of treatment

Patients continued with olaparib until documented disease progression as assessed by the Investigator or unacceptable toxicity or for as long as they did not meet any other discontinuation criteria. Patients continued to receive treatment beyond progression as long as, in the Investigator's opinion, they were benefiting from treatment and they did not meet any other discontinuation criteria. Once patients had been discontinued from study treatment, other treatment options were at the discretion of the Investigator.

Statistical methods

Descriptive and efficacy analyses were summarised for all patients who were assigned to olaparib and safety analyses were summarised for all patients who had received at least one dose of olaparib. The primary endpoint of this study was Investigator-assessed progression-free survival (PFS) according to modified RECIST v1.1 in patients with s*BRCA*m and *BRCA*m ovarian cancer. The PFS was presented as a median with 95% confidence interval (CI), with no formal statistical comparison between patients with s*BRCA*m or g*BRCA*m disease.

Subgroup analyses were performed for the PFS endpoint to assess the consistency of olaparib effect across potential or expected prognostic factors. For each subgroup analysis Kaplan-Meier (KM) curves and median PFS and 95% CI were presented.

All time to event endpoints were described in a similar way to the PFS. A summary of time to Investigator-assessed second progression (PFS2) and overall survival (OS) was produced at the time of the PFS data cut-off (DCO). The Quality of Life (QoL) and safety data were summarised.

The analyses of PFS, OS and safety data were repeated for the exploratory cohort of patients with *BRCA*-independent HRRm^ ovarian cancer.

Subject population

Disposition

The 181 enrolled patients were comprised of 145 patients with *BRCA*m status (87 g*BRCA*m, 55 s*BRCA*m, and 3 patients with germline or somatic mutation status undetermined), 33 patients with HRRm^ disease, and 3 patients enrolled in error (unassigned).

From these 181 patients, 177 were treated with olaparib and were part of the Safety Analysis Set (4 patients withdrew from the study before treatment start).

The g*BRCA*m patient group included 25 patients screened and enrolled under Protocol edition 1 and 62 patients enrolled under subsequent protocol editions. All patients from the s*BRCA*m, HRRm^, undetermined *BRCA*m, and unassigned groups were enrolled under Protocol edition 2 or Protocol edition 3 and their genetic status was determined by central testing.

The median total follow-up time was 2.23 years (range: 0.0-4.6); 2.27 years (range: 0.0-4.6) in the *BRCA*m cohort and 2.06 years (range: 0.1-3.2) in the HRRm^ cohort. At the time of DCO, 59 patients (32.6%) were still receiving study treatment, 4 patients (2.2%) had never been treated with olaparib, and 118 patients (65.2%) had discontinued study treatment; 91 patients (50.3%) in total had terminated the study, and 90 patients (49.7%) in total were still ongoing in the study.

Few patients had important protocol deviations. Furthermore, the outbreak of the COVID-19 pandemic shortly before DCO for this CSR is not judged to have meaningfully impacted the overall quality of the study, including the conduct, data, and interpretation of results.

Demographics

Overall, out of 164 patients with non-missing birth dates (1 site reported year of birth only for 17 patients, and age was not calculated for partial dates), the median age for patients was 62.0 years (range: PPD) in the total patient population, and 61.5 years (range PPD ; data available for 130 patients) in the *BRCA*m cohort. The median age was higher in the s*BRCA*m patients (67.0 years; data available for 51 patients) compared with g*BRCA*m patients (56.0 years; data available for 76 patients). Regarding age distribution, the majority of the *BRCA*m cohort and g*BRCA*m patients (62.3% and 75.0%, respectively), were aged <65 years. Conversely, the majority of s*BRCA*m patients (58.8%) were aged ≥65 years.

Baseline characteristics

In the *BRCA*m cohort (n=145), out of 142 patients with non-missing data, the median time (min-max) from original diagnosis was 3.05 years (1.4-25.3). The majority of patients had a primary tumour of the ovary (n=124; 85.5%), and had tumours that were histologically classified as serous (n=131; 90.3%) and were at International Federation of Gynecology and Obstetrics (FIGO) stage IIIC or IV at original diagnosis (n=93; 64.6%; out of 144 patients with this information); all but one patient (n=144; 99.3%) had a high grade tumour. More than half of the patients had received 2 prior lines of chemotherapy (n=80; 55.6%). More s*BRCA*m patients had received 2 prior lines of chemotherapy than g*BRCA*m patients (61.8% vs. 51.7%).

In the *BRCA*m cohort, 97 patients (77.6%) had a PFI over 12 months to the penultimate platinum-based chemotherapy; this proportion was similar for the g*BRCA*m (n=56, 75.7%) and s*BRCA*m (n=40, 80.0%) patients.

Out of 142 patients with non-missing data, the ECOG PS status at baseline was rated 0 in the majority of patients (n=110; 77.5%). The proportion of patients with ECOG PS of 0 was slightly lower (72.7%) in s*BRCA*m patients, as compared to g*BRCA*m patients (data reported for 86/87 patients, 80.2%).

One hundred forty-one patients (97.2%) reported any medical history, and 76 patients (52.4%) had a family history of cancer; more g*BRCA*m patients had a family history of cancer than s*BRCA*m patients (56.3% vs 47.3%), particularly with respect to breast and ovarian cancer.

HRRm^ cohort

All 33 HRRm^ patients were enrolled based on a negative *BRCA*m test from Myriad Genetics and a positive test from FMI as per the Protocol edition 3. The most frequent non-*BRCA* mutations were reported in *CDK12*, *RAD51C*, *BRIP1*, and *RAD51D* genes.

The median age was 64.0 years (range: PPD) in the HRRm^ cohort.

Out of all HRRm^ patients (n=33), the majority of patients had a primary tumour of the ovary (n=27; 81.8%), and the median time (min-max) from original diagnosis was 3.52 years (1.7-9.4; n=32). The majority of the tumours were histologically classified as serous (n=29; 87.9%) and were at FIGO stage IIIC or IV at original diagnosis (n=20; 64.5%, out of 31 patients with this information). All tumours were high grade. Most patients had received 2 prior lines of chemotherapy (n=18; 54.5%).

The PFI to the penultimate platinum-based chemotherapy was available for 30 of the 33 patients; it was over 12 months for 21 patients (70.0%), and between >6 and <12 months for 9 patients (30.0%). Response to the latest platinum-based line of therapy (available for 32 patients) was CR for 11 patients (34.4%), and PR for 21 patients (65.6%).

The ECOG PS status was rated 0 in the majority of patients (n=20; 64.5%; n=31). All HRRm^ patients (n=33) reported some medical history, and 21 patients (63.6%) had a family history of cancer.

Summary of efficacy results

In the overall *BRCA*m cohort, 88 patients had PFS events (n=145, 60.7% maturity). Median PFS (95% CI) was 18.0 months (95% CI: 14.3-22.1). The median PFS (95% CI) was 16.6 months (95% CI: 12.4-22.2) in the s*BRCA*m patients (n=55, 63.6% maturity), and 19.3 months (95% CI: 14.3-27.6) in the g*BRCA*m patients (n=87, 59.8% maturity). Based on the KM estimates of PFS in the *BRCA*m cohort, 84.9% (95% CI: 77.8-89.9), 67.3% (95% CI: 58.7-74.4), and 50.7% (95% CI: 42.0-58.8) of patients were alive and progression-free at 6, 12, and 18 months respectively; these estimates were similar among g*BRCA*m and

s*BRCA*m patients. The sensitivity analyses of PFS were consistent with the primary analysis results.

Certain prognostic factors were found to influence the PFS: The median PFS for patients who had CR to the previous platinum line (n=75, 53.3% maturity) compared to patients who had PR to the previous platinum line (n=68, 70.6% maturity) was 20.6 months vs. 12.4 months. The median PFS for patients with no evidence of disease at baseline (n=69, 53.6% maturity) compared to patients with non-measurable disease (n=34, 70.6% maturity) and measurable disease (n=40, 67.5% maturity) was 22.1 months vs. 16.4 months and 13.7 months, respectively.

At the time of the DCO, 92 patients (63.4%) had discontinued treatment or died in the *BRCA*m cohort (69.1% in s*BRCA*m, 62.1% g*BRCA*m). Consistent with PFS results, the median TDT was 19.8 months (95% CI: 14.3-23.0) in the *BRCA*m cohort, and 19.0 months (95% CI: 13.5-22.6) in the s*BRCA*m patients. Results for the g*BRCA*m patients were generally consistent with those of the *BRCA*m cohort and s*BRCA*m patients.

Data for the secondary endpoint of overall survival (OS) was approximately 30% mature at DCO. In the *BRCA*m cohort, 29.7% had died and based on KM estimates of OS, 98.6%, 94.9% and 91.2% patients remained alive at 6, 12 and 18 months, respectively. Survival rates were comparable among s*BRCA*m patients (98.2%, 94.5% and 94.5%) and g*BRCA*m patients (98.9%, 95.2% and 88.9%), respectively.

Data for the secondary endpoints of time to second progression (PFS2), time to first subsequent therapy (TFST), and time to second subsequent therapy (TSST) was 36.6%, 39.3% and 30.3% mature in all *BRCA*m patients, respectively.

The median PFS (95% CI) was 16.4 months (95% CI: 10.9-19.3) in the HRRm^ cohort (n=33, 66.7% maturity). Based on the KM estimates of PFS, 80.6% (95% CI: 61.9-90.8), 67.7% (95% CI: 48.4-81.2) and 41.0% (95% CI: 23.6-57.6) patients were alive and progression-free at 6, 12 and 18 months, respectively. At DCO, OS was 30.3% mature, with 10 events of death.

Summary of patient-reported outcomes/quality of life results

In all patient groups, FACT-O TOI scores were maintained during the treatment period, with no clinically meaningful changes from baseline in mean TOI scores observed across treatment visits.

The FACIT-Fatigue scores were maintained over the treatment period in all patient groups, with no clinically meaningful changes occurring across treatment visits.

For all patient groups, the mean FLIE scores showed only small decreases through Week 16, with a return to baseline thereafter, and across all visits, scores remained high, indicating a

low impact of nausea and vomiting on the QoL of the respondents throughout the treatment period.

Summary of pharmacogenetic results

Not applicable.

Summary of safety results

- The safety profile of olaparib was generally consistent in all groups (*BRCA*m cohort, s*BRCA*m and g*BRCA*m patients, HRRm^cohort, and total patient population).

- At the DCO the median total treatment duration was 18.96 months in the *BRCA*m cohort (19.42 months and 17.87 months, respectively, in the g*BRCA*m and s*BRCA*m patients), and 17.71 months for the total population.

- The median RDI was over 95% in all groups (*BRCA*m cohort, s*BRCA*m and g*BRCA*m patients, HRRm^ cohort, and total patient population).

- The nature, incidence, and severity of the AEs was consistent with the established/known safety profile of olaparib; the majority of AEs were of mild or moderate severity.

- Up to the DCO, 166 patients (93.8%) in the total population and 135 *BRCA*m patients (94.4%) had experienced at least one AE (82 g*BRCA*m patients [94.3%] and 52 s*BRCA*m patients [94.5%]).

- The most frequent AEs (presented for ≥20% of the patients) were known ADRs of olaparib and included nausea (53.1%), anaemia (44.1%), fatigue (42.0%), and vomiting (26.6%) in the *BRCA*m cohort. In the total patient population, these proportions were 53.7%, 42.4%, 42.9% and 27.7%, respectively. Those events were typically Grade 1 or Grade 2, and were similarly distributed across the *BRCA*m cohort, s*BRCA*m and g*BRCA*m patients, and in the total patient population.

- The frequency distribution of AEs of CTCAE Grade 3 or higher, SAEs, AEs leading to dose interruption, and AEs leading to permanent treatment discontinuation was similar across patient groups (*BRCA*m cohort, g*BRCA*m and s*BRCA*m subsets, HRRm^ cohort, and the total patient population).

- In the *BRCA*m cohort, AEs of CTCAE Grade 3 or higher were observed in 36.4% of the patients, SAEs in 25.9%, and AEs leading to treatment interruption in 49.7%, and to permanent treatment discontinuation in 4.9% of patients, respectively. In the total patient population, these proportions were 35.0%, 25.4%, 48.6% and 4.5%, respectively.

- Grade 4 AEs were reported by 4 patients in the *BRCA*m cohort and 6 patients in the total population, including anaemia, nausea, small intestinal obstruction, and platelet count decreased in the *BRCA*m cohort, and myocardial infarction and pulmonary embolism in the HRRm^ cohort.

- Anaemia was the most frequent AE of CTCAE Grade 3 or higher (25 *BRCA*m patients [17.5%] and 28 patients [15.8%] in the total population) and the most common SAE (11 *BRCA*m patients [7.7%] and 12 patients [6.8%] in the total population); however, discontinuation of the treatment due to anaemia was required for 1 patient only (*BRCA*m cohort, 0.7%).

- There were 4 AESIs in 4 patients, all in the *BRCA*m cohort, including 2 cases of AML, and 2 cases of new primary malignancy (Burkitt's lymphoma and papillary thyroid cancer); there were no events of pneumonitis.

- Four TEAEs (all in g*BRCA*m patients) had an outcome of death, including AML (n=2), Burkitt's lymphoma, and sudden death.

- The most common AE leading to dose interruption was anaemia, in both the *BRCA*m cohort (n=29, 20.3%) and in the total patient population (n=32, 18.1%), followed by vomiting (*BRCA*m: n=10, 7.0%; total patient population: n=12, 6.8%).

- Eight patients in total (4.5%), of which 7 patients (4.9%) in the *BRCA*m cohort, experienced 11 AEs leading to permanent treatment discontinuation, including diarrhoea (n=2), AML (n=2), anaemia, neutropenia, thrombocytopenia, fatigue, dysarthria, anxiety, and small intestinal obstruction (n=2).

- Changes in laboratory parameters during the treatment period were evidenced for haemoglobin and platelet count, which decreased over time; erythrocyte mean corpuscular volume (increasing throughout the treatment period), creatinine and bilirubin (both slightly increased). The erythrocyte mean corpuscular volume and blood creatinine had not completely returned to the baseline level 30 days after discontinuation of the treatment by olaparib.

- No hepatobiliary or renal safety concerns were identified from review of the laboratory and AE data. No potential Hy's law case was identified in this study.

Conclusions

- Maintenance therapy with olaparib capsules demonstrated consistent clinical activity on Investigator-assessed PFS by modified RECIST version 1.1 in *BRCA*m and s*BRCA*m platinum sensitive relapsed ovarian cancer patients.

- The median PFS (95% CI) in the overall *BRCA*m cohort (n=145, 60.7% maturity) was 18.0 months (95% CI: 14.3-22.1); the median PFS (95% CI) was 16.6 months (95% CI: 12.4-22.2) in the s*BRCA*m patients (n=55, 63.6% maturity), and 19.3 months (95% CI: 14.3-27.6) in the g*BRCA*m patients (n=87, 59.8% maturity).

- Certain prognostic factors were found to influence the PFS. Median PFS was notably longer (>6 months) in patients with CR (vs. PR), and in patients with no evidence of disease at baseline (vs. non-measurable disease and measurable disease, respectively).

- Overall survival, TFST, TSST and PFS2 data were immature at DCO. Kaplan-Meier estimates at 6, 12 and 18 months were generally similar in the *BRCA*m cohort, s*BRCA*m and g*BRCA*m patients for these endpoints.

- The QoL of patients was maintained during the treatment period, with no clinically meaningful detriments observed across treatment visits. Findings were similar for the *BRCA*m cohort and the s*BRCA*m and g*BRCA*m patients.

- The safety and tolerability of olaparib observed in this study was generally consistent in the *BRCA*m, s*BRCA*m and g*BRCA*m patients, the HRRm^ cohort, and the total patient population, and was in line with the known safety profile of olaparib used in monotherapy.

- The most frequent mutations observed in the exploratory HRRm^cohort concerned the *CDK12*, *RAD51C*, *BRIP1*, and *RAD51D* genes.

- Patients from the HRRm^ cohort had baseline characteristics and clinical outcomes comparable to those of patients with *BRCA*m disease.