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Pharmacokinetic Profile of Intramuscular Fulvestrant in Advanced Breast Cancer

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Abstract

Objective: To characterise the pharmacokinetics of a long-acting formulation of fulvestrant following intramuscular administration of single and multiple doses.

Study design: Pharmacokinetic investigations of single and multiple doses of fulvestrant were conducted within two global phase III efficacy studies that compared intramuscular fulvestrant with oral anastrozole in postmenopausal women with hormone-sensitive advanced breast cancer (study 0020, conducted in Europe, Australia and South Africa, and study 0021, conducted in North America).

Methods: Patients received once-monthly intramuscular injections of fulvestrant 250mg (1 × 5mL for ≤21 months in study 0020; 2 × 2.5mL for ≤30 months in study 0021). Serial blood samples were collected for the first 28 days after the initial dose and immediately prior to all subsequent monthly doses. Plasma fulvestrant concentrations were determined by high-performance liquid chromatography-tandem mass spectrometry.

Patients: Twenty-six (study 0020) and 193 (study 0021) postmenopausal women, comprising the pharmacokinetic subgroups of the phase III efficacy trials, were studied. Patients had shown disease progression or recurrence following previous hormonal therapy for advanced disease or had relapsed after adjuvant endocrine therapy with a nonsteroidal antiestrogen.

Outcome measures and results: For single-dose fulvestrant 250mg, area under the concentration-time curve from time zero to 28 days (AUC_{28}), maximum observed plasma concentration (C_{max}), minimum observed plasma concentration at 28 days (C_{min}) and time to maximum plasma concentration (t_{max}) were determined. For multiple-dose fulvestrant 250mg once monthly, steady-state trough concentrations (C_{trough}) were determined. Plasma fulvestrant concentra-

tions reached a peak at a median of 7 days (range 2–8 days) postdose, and declined biexponentially with a slower phase commencing approximately 2–3 weeks postdose. Intersubject variability in C_{max} and AUC_{28} was approximately 6-fold and 4-fold, respectively. Mean parameters for single-dose fulvestrant were: AUC_{28}, 148 μg • day/L; C_{max}, 8.2 μg/L; C_{min}, 2.6 μg/L; t_{max}, 7.0 days. Geometric mean C_{trough} increased from 2.57 to 6.15 μg/L (study 0020) and from 2.38 to 6.52 μg/L (study 0021) over the first 6 months, reaching steady-state concentrations of approximately 6–7 μg/L (study 0020) or 9 μg/L (study 0021). Preliminary pharmacokinetic analysis, using a naive pooled data approach, suggests that observed single- and multiple-dose plasma profiles can be adequately described with a two-compartment kinetic model. Model-generated steady-state AUC_{28} values were approximately 300 μg • day/L.

Conclusions: The intramuscular formulation of fulvestrant displays predictable kinetics and approximately 2-fold accumulation on administration once monthly. At the proposed therapeutic dosage (250mg once monthly), plasma fulvestrant concentrations are maintained within a narrow range throughout the administration interval, thus ensuring stable systemic drug exposure during long-term treatment.

Fulvestrant (Faslodex®)[1], a new estrogen receptor (ER) antagonist, is now available for the treatment of hormone receptor-positive metastatic breast cancer in postmenopausal women that has progressed during prior antiestrogen therapy. Fulvestrant acts by blocking ER transcriptional activities and downregulating cellular levels of the ER.[1-3] Unlike the nonsteroidal antiestrogens (e.g. tamoxifen, toremifene and raloxifene), which display mixed estrogen antagonist and agonist properties,[4,5] fulvestrant causes complete abrogation of estrogen-sensitive gene transcription and has no known estrogen agonist effect.[6] Fulvestrant has a unique mode of action that offers the potential for continued hormonal treatment in patients with advanced, hormone-sensitive breast cancer that has progressed with tamoxifen treatment. The efficacy of fulvestrant in this treatment setting has been confirmed in a phase II clinical study, where women treated with fulvestrant achieved a clinical benefit rate of 69% after disease progression with tamoxifen treatment.[7] Fulvestrant also offers potential therapeutic advantages over aromatase inhibitors in the postmenopausal setting as, unlike aromatase inhibitors, it is able to block the trophic effects of exogenous estrogens. In two global phase III studies carried out in postmenopausal women with advanced, tamoxifen-resistant breast cancer (trial 0020, conducted in Europe, South Africa and Australia, and trial 0021, conducted in North America), fulvestrant was similar to anastrozole for the primary efficacy endpoint, time to progression (median 5.5 vs 5.1 months [trial 0020] and 5.4 vs 3.4 months [trial 0021] for fulvestrant and anastrozole, respectively). Secondary endpoints included objective response rate, clinical benefit rate and median duration of response, which were not significantly different between the two treatment groups. In both trials, fulvestrant and anastrozole were equally well tolerated.[8,9]

Fulvestrant has low aqueous solubility and has been developed as a long-acting, oil-based formulation for use as a once-monthly intramuscular injection. This parenteral depot formulation provides adequate bioavailability and offers potential compliance advantages over existing breast cancer treatments. Intramuscular administration can offer sustained plasma drug concentrations, and will also

1 The use of trade names is for product identification purposes only and does not imply endorsement.

be less affected by vomiting and subsequent tablet loss than oral agents. Preliminary findings in postmenopausal women with primary breast cancer indicate that slow-release intramuscular fulvestrant exhibits linear kinetics over the dose range 50–250mg following single-dose administration.[10]

The aim of the present series of investigations, conducted within the confines of the phase III clinical trial programme, was to characterise the pharmacokinetic profile of fulvestrant after single and multiple doses.

Materials and Methods

Patients

Both studies recruited postmenopausal women with hormone-sensitive advanced breast cancer who had experienced either disease recurrence or progression following previous hormonal therapy for advanced disease or whose disease had relapsed following adjuvant endocrine therapy with a non-steroidal antiestrogen. Patients were defined as hormone sensitive if they: (i) had received ≥12 months of adjuvant hormonal therapy before relapse; (ii) had shown ≥3 months of tumour remission or stabilisation following hormonal therapy; or (iii) were ER positive or progesterone receptor (PgR) positive.

Patients who had received more than one prior endocrine treatment for advanced breast cancer were excluded from the studies, as were those with severe/uncontrolled systemic disease or hepatic impairment (total bilirubin >1.5 times the upper limit of normal [ULN]; alanine aminotransferase [ALT] or aspartate aminotransferase [AST] >2.5 times the ULN in the absence of hepatic metastasis; or ALT or AST >5 times the ULN in the presence of hepatic metastasis). Patients with a history of treatment with fulvestrant or an aromatase inhibitor, or recent exposure to extensive radiotherapy, cytotoxic therapy, estrogen replacement therapy, any non-approved drug (within 4 weeks) or a luteinising hormone-releasing hormone (LHRH) analogue (within 3 months) were also excluded from study participation. Initiation of corticosteroids, adrenocortical suppressants, low-dose progestins or ketoconazole was not permitted during the studies, but continuation of existing treatment with these agents was allowed at the investigator's discretion.

The studies were approved by the relevant local ethics committees and were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each patient prior to study entry. Efficacy and tolerability findings from these studies are reported elsewhere.[8,9]

Pharmacokinetic Study Design

European Study (0020)

A randomised, open-label, parallel-group study, conducted primarily in Europe, Australia and South Africa, investigated the plasma kinetics of fulvestrant following single monthly (28 ± 3 days) intramuscular injections of fulvestrant 250mg, administered in a total volume of 5mL into the gluteus maximus muscle. Serial blood samples were collected for the first 28 days of treatment and single blood samples were obtained before each subsequent dose, for a period of ≤21 months.

North American Study (0021)

A randomised, double-blind, parallel-group study conducted in North America investigated the plasma kinetics of fulvestrant following single monthly (28 ± 3 days) intramuscular injections of fulvestrant 250mg, administered in two 2.5mL injections (one in each buttock). To preserve study blindness, matching anastrozole placebo tablets were supplied for once-daily oral administration. Serial blood samples were collected for 28 days after the first dose and single blood samples were obtained before each subsequent dose, for a period of ≤30 months.

Pharmacokinetic Assessments

Serial blood samples (10mL) for pharmacokinetic analyses were collected predose and at 3 hours and (at any time) 1, 2, 7, 10, 14, 21 and 28 days after the first dose of fulvestrant. A further blood sample was collected 21 days after the third dose of fulves-

trant (study 0021 only). In addition, predose (trough) blood samples (10mL) were taken immediately before each monthly fulvestrant injection for the duration of each study. Samples were collected in lithium-heparin tubes and centrifuged for 10 minutes at 1000*g* within 10–15 minutes of blood sampling. The plasma was immediately separated, frozen and stored at −20°C until required for analysis.

Assay Method

Plasma fulvestrant concentrations were determined by means of a validated highly sensitive and specific high-performance liquid chromatography (HPLC)-tandem mass spectrometry method, using deuterated fulvestrant as the internal standard. Fulvestrant was extracted from a 0.5mL heparinised plasma sample using 2mL of 10% (v/v) hexane/2-propanol and, following centrifugation, the organic layer was evaporated to dryness under a stream of nitrogen at 40°C. The dry residue was reconstituted in 200µL of methanol/water (5 : 1 v/v) and a 20µL aliquot was injected onto a 5cm × 4mm Inertsil® C18 HPLC column (GL Sciences, Inc., Tokyo, Japan) and eluted at a flow rate of 0.7 mL/min. Detection was performed with a Sciex API III+® triple quadrupole mass spectrometer (Perkin-Elmer, Boston, MA, USA) in positive multiple reaction mode (MRM). The following ions were selected for measurement (precursor/product transitions): m/z 607→589, the product ion of fulvestrant, was measured against that of the m/z 613→595 product ion of the [$^2H_6$]fulvestrant internal standard.

Concentrations of fulvestrant were calculated from peak area ratios (fulvestrant/internal standard) by reference to calibration series constructed by adding known amounts of fulvestrant (0.25–50 µg/L) to control plasma and extracting these standards in parallel with the test samples. Quantification was performed using a weighted (1/concentration^2) least squares linear regression line generated from the standard samples. No samples with concentrations higher than the top standard were found, and dilution into the working range with blank plasma was therefore not necessary. The performance of the assay was monitored throughout use by inclusion of quality control samples prepared at low, medium and high concentrations in blank human plasma, and analysed in duplicate with each batch of sample analysis. The acceptance/rejection criteria were based upon a coefficient of variation (CV) of 20%. The lower limit of quantification of the assay was 0.25 µg/L, while assay precision, expressed as the intra- and inter-assay coefficients of variation (CV%), at this level were 19.5% and 16.2%, respectively, and both generally ≤7% at the higher concentrations (as assessed in study 0021). Accuracies were 97.3–109% of the theoretical concentrations for the three quality control standards.

Pharmacokinetic Analysis

The maximum observed plasma concentration (C_{max}), time to reach the maximum plasma concentration (t_{max}) and minimum plasma concentration (C_{min}) during the 28-day period after the first dose were determined from the individual plasma concentration-time profiles. In the multiple-dose studies, trough plasma concentrations (C_{trough}) were determined directly from blood samples collected immediately prior to each monthly injection. The plasma concentration-time data for fulvestrant were analysed by non-compartmental methods using validated software (WinNonlin version 1.5; Scientific Consulting, Cary, NC, USA). The area under the concentration-time curve from time zero to 28 days (AUC_{28}) [±2 days] after the first dose was calculated using the linear trapezoidal method. Estimates of accumulation, time to steady state and the plasma elimination half-life ($t_{½\beta}$) were obtained using pharmacokinetic models, with first-order input and distribution, fitted to the single-dose plasma concentration-time data and also to the multiple-dose C_{trough} data from each trial by using a naive pooled data approach (i.e. it was assumed that all the plasma concentrations came from the same patient). The data were analysed using WinNonlin with 1/y weighting. Model-generated pharmacokinetic parameter estimates were compared for the single and multiple doses.

Statistical Analysis

Data were analysed descriptively and, for parameters with a log-normal distribution, C_{max}, C_{min}, C_{trough} and AUC_{28} values were summarised as the

geometric mean, CV, range and standard deviation. The t_{max} values were summarised as the median and the range. The geometric mean was calculated as exp (μ) and the CV was calculated as (equation 1):

$$CV\% = 100 \times \left[\exp\left(\sigma^2\right) - 1\right]^{1/2} \quad \text{(Eq. 1)}$$

where μ and σ^2 are the mean and variance of the log-transformed data. In those instances where ≤50% of plasma fulvestrant concentrations were non-quantifiable at a given timepoint, the geometric mean and CV were calculated by substituting the limit of quantification (0.25 μg/L) for the missing values. If >50% of plasma concentrations were non-quantifiable, the geometric mean and CV values were reported as unknown.

Results

Patient Demographics

The baseline demographic and clinical characteristics of the two study populations are summarised in table I. Plasma samples for determination of the single-dose kinetic profile of fulvestrant were obtained from 16 of 222 patients randomised to receive the drug in study 0020 and from four of 206 patients who received the drug in study 0021. However, in view of the limited size of this latter patient cohort, single-dose data are given for indicative purposes only. Trough plasma samples for determination of the multiple-dose kinetic profile were obtained from 26 and 193 patients in studies 0020 and 0021, respectively. Both study cohorts had a mean age of 63 years and mean bodyweights were similar: 69kg and 72kg for studies 0020 and 0021, respectively. The majority of patients were Caucasian, although the North American cohort included 10% Black and 4% Hispanic patients.

Table I. Baseline demographic and clinical characteristics of trial 0020 and 0021 study populations

Characteristic	Study 0020 (n = 26)	Study 0021 (n = 193)
Age at entry (years)[a]		
mean (SD)	62.9 (10.0)	63.2 (11.2)
median	61	64
range	43–85	33–89
Weight at baseline (kg)[a]		
mean (SD)	68.1 (9.8)	71.2 (14.2)
median	69.0	72.1
range	40.9–81.2	39.5–126.8
Race (%)		
White	100	85.5
Black	0	9.8
Hispanic	0	4.1
other	0	0.5
Hormone receptor status (%)		
ER+ and/or PgR+	84.6	86.5
ER–and/or PgR–[b]	0	6.7
ER and PgR status unknown	15.4	6.7
WHO performance status at baseline (%)		
0	46.2	46.1
1	50.0	43.5
2	3.8	10.4
Local regional radiotherapy (%)	73.1	47.7
Radiotherapy for metastasis (%)	19.2	31.6
Cytotoxic chemotherapy (%)	38.5	63.2
Adjuvant hormonal treatment (%)		
yes (<12 months to relapse)	3.8	8.3
yes (≥12 months to relapse)	42.3	50.3
no	53.8	41.5
Hormonal treatment for advanced breast cancer (%)		
yes (remission for ≥3 months)	65.4	51.8
yes (remission for <3 months)	0	2.6
no	34.6	45.6

a Data for n = 25 and n = 188, respectively.

b ER negative and PgR negative, or ER negative and PgR unknown, or ER unknown and PgR negative.

ER = estrogen receptor; **PgR** = progesterone receptor.

Single-Dose Pharmacokinetics

Following the first dose of intramuscular fulvestrant, the time needed to achieve peak plasma concentrations indicated prolonged release of fulvestrant from the injection site (t_{max} generally varying between 2 and 8 days). Thereafter, the concentrations declined slowly to about a quarter of the maximum by 28 days after administration. Individual plasma concentration-time profiles demonstrated some interpatient variability in trial 0020; C_{max} and AUC_{28} values ranged from 3.8 to 23.8 μg/L and 73 to 309 μg • day/L, respectively, in studies 0020 and

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