25 May 2023
EMA/428048/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vivjoa

International non-proprietary name: oteseconazole

Procedure No. EMEA/H/C/005682/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AUC_{0-24}	area under the plasma drug concentration versus time curve from 0 to 24 hours
AUC_{ext}	extrapolated area under the plasma drug concentration versus time curve from time of last measured concentration to infinity
AUC_{inf}	area under the plasma drug concentration versus time curve from Time 0 extrapolated to infinity
AUCτ	area under the plasma concentration-time curve from time zero to time t
BMI	body mass index
bid	twice-daily
CL/F	apparent clearance (F represents bioavailability of total daily dose)
C_{max}	maximum concentration
CSR	clinical study report
CYP51	CYP51 enzyme (lanosterol demethylase)
DDI	drug-drug interaction
EE	ethinyl estradiol
ECG	electrocardiogram
ESRD	end stage renal disease
IMP	investigational medicinal product
ITT	Intent-to-Treat
KOH	potassium hydroxide
MCS	mental component score
NE	norethindrone
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
PK	pharmacokinetic
PKE	pharmacokinetic evaluation
PP	Per Protocol
qd	once-daily
qw	once-weekly
RVVC	recurrent vulvovaginal candidiasis
SAE	serious adverse event
SF-36	36-item Short Form Survey
SOC	System Organ Class
$t_{1/2}$	terminal elimination half-life
TEAE	treatment emerged adverse event
T_{lag}	lag time for absorption after dosing
T_{max}	time to maximum concentration
TOC	test of cure
VVC	vulvovaginal candidiasis
V_zF	apparent volume of distribution

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the application for Vivjoa (oteseconazole) in the *treatment and prevention of recurrent vulvovaginal candidiasis (RVVC) including the acute episode of RVVC in adult women* is ***not approvable*** since Major Objections have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions.

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions.

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

Quality

The omission of controls for the identified azoxy compounds is not yet acceptable.

Clinical

The use of oteseconazole (600 mg on day 1 and 450 mg on day 2) to treat AVVC episodes in women with a history of RVVC is not adequately supported by the evidence. The indication should be reworded exactly and only as follows: Vivjoa *is indicated for prevention of acute vulvovaginal candidiasis (AVVC) in adult female patients with no childbearing potential who have a history of recurrent vulvovaginal candidiasis (RVVC).*

The applicant's proposal to advise that recipients should avoid pregnancy via assisted reproduction methods (and hence inevitably avoid breastfeeding) for 2 years and 8 months from start of treatment is not acceptable. The time limit must be removed from the contraindication and the contraindication remaining should refer only to WOCP.

1.1. Questions to be posed to additional experts

None

1.2. Inspection issues

1.2.1. GMP inspection(s)

None

1.2.2. GCP inspection

None

1.3. New active substance status

Based on the review of the data, it is considered that the active substance oteseconazole contained in the medicinal product Vivjoa is qualified as a new active substance.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

The proposed indication for oteseconazole is *for the treatment and prevention of recurrent vulvovaginal candidiasis (RVVC) including the acute episode of RVVC in adult women*.

RVVC has been defined in literature as at least three or four symptomatic episodes in the previous 12 months. While the applicant applied a definition of at least three prior attacks within 12 months to the selection criteria in clinical efficacy studies, certain guidelines apply a definition of at least four such attacks. In two sponsor-commissioned surveys, each consisting of more than 200 women with at least three infections in the past 12 months, no difference was observed in quality of life and impact on life metrics between women experiencing three vs. four episodes of VVC within 12 months.

2.1.2. Epidemiology

VVC is a global health condition that affects approximately 75% of women at least once in their lifetime, most commonly when they are of childbearing age. Approximately half of these women experience a recurrence and 5-9% of those with recurrence develop RVVC.

2.1.3. Aetiology and pathogenesis

VVC is an infection of the vagina and vestibule that can spread outside the labia to the perianal region. Between 70–90% of VVC cases are caused by *Candida albicans*, with infections caused by *C. glabrata* accounting for 10–20%. Less frequently, *C. krusei, C. parapsilosis* and *C. tropicalis* have been reported as the causative pathogen.

Since oestrogen is known to increase the glycogen concentration of the vaginal lining and as glycogen is a substrate on which *C. albicans* thrives, VVC infections are lower in pre-menarche and postmenopausal female subjects and highest in women of childbearing potential (WOCP). However, postmenopausal women taking hormone-replacement therapy may have a similar risk to WOCP. Additional predisposing factors for VVC include lowered immunity due to HIV, steroid therapy, uncontrolled diabetes, sexual activity with an infected partner, use of oral or some barrier forms of contraception and recent use of antibacterial agents.

2.1.4. Clinical presentation, diagnosis

Primary symptoms of VVC include itching/burning, irritation, inflammation, abnormal vaginal discharge, dysuria and painful sexual intercourse. In patients with recurrent infections, distressing physical symptoms are compounded by emotional and psychological suffering.

2.1.5. Management

Acute VVC can be treated locally with topical imidazole derivatives (e.g. clotrimazole). Alternative treatment options for non-pregnant women are oral triazoles (e.g. fluconazole).
Uncomplicated acute VVC is typically treated with a short-course topical agent for 1-7 days or a single oral dose of fluconazole. These regimens provide a clinical and mycological cure rate of approximately 80%.

These treatment approaches are often insufficient for RVVC. In Europe, fluconazole is indicated for prophylaxis to reduce the incidence of recurrent vaginal candidiasis using fluconazole 150 mg on days 1, 4 and 7 followed by 150 mg once weekly for 6 months. Sobel *et al*. reported that within 6 months of completing such a course of fluconazole a recurrence occurred in 57%, with about half of cases having onset within 3-4 months.

2.2. About the product

Oteseconazole (VT-1161) is a tetrazole inhibitor of fungal lanosterol demethylase (CYP51) that has been evaluated for the treatment of the acute episode of VVC and prevention of recurrence of VVC in women who have a history of RVVC. It is presented for clinical use as 150 mg hard capsules.

2.3. The development programme/compliance with guidance/scientific advice

CHMP scientific advice was obtained on four occasions. Only one of these involved the clinical development programme (2018) and this was a joint CHMP/HTA procedure resulting in two separate response letters. The others were quality only (2) or nonclinical only (1).

The main features of the joint CHMP/HTA advice pertaining to the clinical aspects, which concerned only CL-011 and -012 (CL-017 was not planned at that time and was never discussed with CHMP), addressed issues that included the following:

- The CHMP recommended that a renal impairment study should be conducted that assessed effects on free oteseconazole. The applicant did conduct a study but free oteseconazole was not estimated.
- A DDI study with a COC was recommended; this was done.
- The definition of RVVC based on at least 3 episodes within one year was deemed acceptable.
- A screening score at least 3 was accepted but it was recommended that the score at randomisation should be zero or 1. The applicant did not adopt this to define the primary analysis population but did present and describe recurrence rates for the subsets with a score of zero at randomisation.
- The CHMP found no scientific rationale for the dose but agreed that the dose was to some extent supported by the Phase 2 study CL-006.
- Comparison with placebo was deemed appropriate.
- The primary endpoint was deemed acceptable; suggestions were made for additional secondary analyses, which have been conducted.
- The CHMP did not support the plan to use multiple imputation but did recommend a missing=failure approach. The applicant did apply MI but also presented M=F analyses in a descriptive fashion.
- The CHMP questioned the plan to describe susceptibility to oteseconazole. The applicant did not satisfactorily address this matter.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

A QP declaration confirming that the active substance has been manufactured in accordance with GMP has been provided from the proposed batch release site. The Applicant has clarified that the auditor and the auditee belong to the same mother company. Hence, the absence of conflict of interest between these sites has not been demonstrated. However, the compliance with GMP of the

micronisation site is not questioned since a GMP certificate for this operation has been issued by the Hungarian authority. This issue will no longer pursued.

GLP

The applicant has provided a summary table of Good Laboratory Practice (GLP) compliant studies conducted in support of oteseconazole in an annex to the cover letter. This table indicates that pivotal repeat-dose toxicity studies of up to 26-weeks duration in rats and 39 weeks in dogs, the standard battery of genotoxicity studies, a full reproductive and developmental toxicity package in rats and rabbits, carcinogenicity studies in rats and transgenic mice, and a phototoxicity study in rats were conducted in compliance with the principles of GLP at a facility/ test site that was at the time of study completion part of an OECD MAD GLP monitoring programme. The accompanying study reports include GLP compliance statement signed by the study director.

GCP

The Clinical Overview contains the following statement:
All studies were undertaken in accordance with standard operating procedures, which comply with the principles of Good Clinical Practice. All studies were conducted with the approval of Institutional Review Boards. Informed consent was obtained for all patients, and the studies were performed in accordance with the ethical principles originating from the Declaration of Helsinki.

2.5. Type of application and other comments on the submitted dossier

2.5.1. Legal basis

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application. The application is made under Article 3(2)(a), optional use of the centralised procedure for a new active substance (NAS).

2.5.2. New active substance status

The applicant requested the active substance oteseconazole contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

2.5.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision on the agreement of a paediatric investigation plan (PIP), Decision number P/0460/2021. The granting of a product-specific waiver concerned all male subjects and female subjects aged from birth to 12 years.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred, i.e. regarding use in adolescent female subjects aged 12-<18 years, which is to be based on an extrapolation exercise.

The PDCO issued a positive opinion on compliance for the PIP.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The drug substance, oteseconazole, is obtained by chemical synthesis.

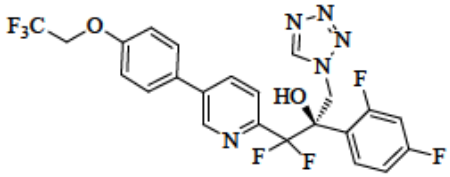
The finished product is a hard capsule containing 150 mg of the drug substance.

3.1.2. Active substance

The full module 3.2.S has been provided in the dossier.

3.1.2.1. General Information

Oteseconazole is the INN for (2R)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(tetrazol-1-yl)-1-[5-[4-(2,2,2-trifluoroethoxy)phenyl]pyridin-2-yl]propan-2-ol, an antifungal agent which has the following structure:



It is a white/almost white solid substance. Oteseconazole contains a single chiral centre and it is manufactured as the R-enantiomer. It is practically insoluble or insoluble in aqueous media over the pH range 1.0-11.0 and soluble/freely soluble in a variety of organic solvents. Oteseconazole exhibits polymorphism.

3.1.2.2. Manufacture, process controls and characterisation

The manufacturing process includes several synthetic steps and salt formation steps. The micronised oteseconazole is defined as the finished drug substance.

The narrative description of the manufacturing process includes sufficient details on the quantities of starting materials, reagents, catalysts and solvents, on the operative conditions and on the in-process controls. The reprocessing procedures are well detailed. The commercial batch size(s) of the finished API is indicated in the dossier.

Information about the suppliers, method of manufacturing and the origin and fate of impurities has been presented for each starting material.

The in-process controls performed during the synthesis of oteseconazole are justified based on the description of the development of the manufacturing method provided in section 3.2.S.2.6 of the dossier. The specifications applied to the isolated intermediates are generally acceptable and supported by exemplary certificates of analysis.

The Applicant has stated that process validation is in progress and has confirmed that the manufacturing process of oteseconazole active substance will be validated before commercial distribution of the drug product.

The development of the manufacturing process has been satisfactorily described. The commercial process is essentially the same as that used for the manufacturing of the clinical batch.

The critical aspects for each manufacturing steps have been described. Proven acceptable ranges (PAR) have been established for each of the identified critical variables, based on a design-of-experiment approach or by performing traditional single experiments.

The proposed structure of oteseconazole has been satisfactorily confirmed with a variety of techniques.

A comprehensive polymorphic screening was performed on the finished drug substance.

Single crystal x-ray diffraction analyses have confirmed the R absolute configuration of the chiral centre in oteseconazole.

A comprehensive list of impurities and by-products that can be originated from starting materials or can be formed during the synthetic process has been given in the context of the discussion on potential mutagenic impurities. The fate of the majority of the impurities that have been identified as class 5 in accordance with the ICH M7 classification has been discussed and the omission of controls for these impurities has been justified.

The control strategy for residual solvents and elemental impurities is generally adequate and in line with current guidance.

The control strategy for the identified mutagenic impurities has been revised. The maximum allowed concentrations for mutagenic impurities have been corrected where applicable and the omission of control limits for these impurities have been generally justified on the basis of confirmatory testing on the finished API and/or of suitable intermediates. In some cases, predicted purge factors have been used, which have been accepted given that these are significantly larger that the required purge factors. An **OC** remains outstanding for the purge factor predicted for an impurity.

The proposed route of synthesis gives rise to the potential formation of mutagenic impurities which can form during the manufacturing steps. The omission of controls for these impurities is not accepted at this time and, depending on the revised control startegy, additional confirmatory testing should be performed **(MO)**.

The **MO** in relation to the addition of control limits for total mutagenic impurities has been maintained, as the omission of controls for several azoxy compounds has not yet been accepted.

A discussion on the presence of nitrosamine impurities in the finished drug substance has been presented. The omission of controls for these N-nitrosmaine impurities is justified.

Validation data of the analytical methods used for the determination of the residual levels of known/potential mutagenic impurities have been provided, however data are missing for some of the methods **(OC)**.

3.1.2.3. Specification, analytical procedures, reference standards, batch analysis, and container closure

The specification applied to oteseconazole by the drug substance manufacturer generally covers relevant parameters for an active substance for pharmaceutical use.
The specification applied to oteseconazole by the drug product manufacturer is in line to that applied by the drug substance manufacturer.

The description and the validation of the analytical procedures used for the control of the drug substance are acceptable. The stability-indicating nature of the methods used for the determination of assay and related substances has been demonstrated.

Adequate information has been provided for the reference standards used by the drug substance manufacturer.

The specification, exemplary certificate of analysis and statements of compliance with Ph. Eur. standards and with Commission Regulation (EU) No 10/2011 as amended have been provided for the primary container. The specification applied to the primary container used for the storage of the unmicronised oteseconazole should be provided in the English language **(OC)**.

Stability studies have been conducted in line with ICH guidance. The studies at accelerated stability conditions have been completed, whereas the long-term stability data cover 12 to 36 months. All the batches complied with the proposed specification at both storage conditions. There was no significant change in the tested parameters and no specific trend can be identified. Based on the available stability data, the proposed retest period of 24 months is accepted. No special storage conditions are required.

A post approval change management protocol (PACMP) has been proposed. The PACMP is acceptable.

3.1.3. Finished Medicinal Product

3.1.3.1. Description of the product and Pharmaceutical Development

Description of the product

Oteseconazole 150 mg capsule, hard is gelatin, tubular, size No. 2 capsule of pink colour (cap and body) with black imprinting "RG" in circle (cap) and "150" (body).

The composition includes the following excipients: Silicified microcrystalline cellulose, Lactose monohydrate, Hydroxypropylcellulose, Croscarmellose sodium, Sodium laurilsulfate, Magnesium stearate, Capsule gelatin hard.

The properties of the drug substance and excipients have been sufficiently explained. The excipients used are well known and commonly used, their functions have been described and their general compatibility with each other and the drug substance has been deemed acceptable.

The choice of dissolution method is considered appropriately justified. The evaluation of discriminatory power shows that the chosen dissolution method is discriminatory. However, a major objection is raised on the routine dissolution limit, refer to section 3.2.P.5.

Bioequivalence study/ dissolution profiles

In order to prove bioequivalence between Oteseconazole 150 mg capsule, hard manufactured at the commercial manufacturing site and Oteseconazole 150 mg capsule, hard used in Phase 3 clinical studies**,** the following bioequivalence study was also conducted: *A Single Dose, Open Label, Balanced, Randomized, Parallel, One-Period, Two-Treatment Comparative Oral Bioavailability Study Comparing Two Formulation of Oteseconazole 150 mg Capsule In Healthy Men And Women With Non-Childbearing Potential, Under Fed Condition*. The bioequivalence criteria are met. Please refer to the clinical assessment report for further details.

The choice of manufacturing process has been justified. The process is considered standard and a well-known process for the production of capsules. The level of justification provided is deemed acceptable on this basis. The critical process parameters have been identified and are outlined in section 3.2.P.3.4. The parameters chosen were found satisfactory during development batches.

Oteseconazole 150 mg capsule, hard are packed into the following packaging materials:
- colourless PVC/PE/PVDC foil and silver Aluminium foil, hard - PVC/PE/PVDC/AL
or
- colourless PVC/Aclar/PVC foil and silver Aluminium foil, hard- PVC/ACLAR/PVC/AL
or
- silver Aluminium foil and silver Aluminium foil, hard - AL/AL.

The blister packaging proposed is standard for hard capsules. All packaging complies with EU guidelines. However, some other concerns are raised on packaging, see below and section 3.2.P.7.

3.1.3.2. Manufacture of the product and process controls

Manufacturers and Batch Formula

The manufacturers are acceptable, valid GMP certificates have been provided. Clarifications on the QP declaration have been requested, refer to section 2.4 of this Overview.

Flow chart of the manufacturing process and process controls

This is a straight-forward standard manufacturing process. The steps are sufficiently described and controlled.

The in-process parameters and acceptance criteria are acceptable. The tests for control of critical process parameters are acceptable.

Holding time study results for intermediates are shown in 3.2.P.2. The hold times are acceptable based on stability data provided.

Process Validation

This is considered a standard manufacturing process with a high active substance content. As per the EMA Guideline on process validation for finished products - information and data to be provided in regulatory submissions process validation is not required for all batch sizes. Process validation is provided for the pilot scale only and the two commercial scale batches will be validated prior to commercialisation. The process validation protocol for the commercial scale batches is in section 3.3.R and is acceptable.

3.1.3.3. Product specification, analytical procedures, batch analysis

Release and shelf-life specifications

The tests proposed on the specification are considered appropriate for the dosage form and route of administration in order to control the efficacy and safety of the drug product for routine production batches. The related substances limits are in line with ICH Q3B and can be accepted without further discussion.
The proposed dissolution limit has been further justified and is accepted.

All analytical procedures are sufficiently described and validated. It is noted that a non-specific UV method is used for assay. This is acceptable as per ICH Q2 as a specific method is used for related substances (chromatographic purity). The information provided on reference standards by the drug substance and the drug product manufacturer is satisfactory.

Batch data is provided on 3 batches, all results are within specification. The batches provided are consistent with each other indicating a manufacturing process which is under control.

The elemental impurities risk assessment states that the levels of elemental impurities in the drug product are below the ICH PDEs (30% of ICH limits). Confirmatory testing has also been performed. The assessment is satisfactory.

A discussion on the presence of nitrosamine impurities in the finished product has been presented. All the potential sources of contamination have been considered. A statement clearly indicating that no risk of contamination with N-nitrosamine impurities has been identified, in line with the template available on the EMA website, should be provide **(OC)**.

The blister packaging proposed is standard for hard capsules. All packaging complies with EU guidelines.

3.1.3.1. Stability of the product

The stability studies have been carried out in line with ICH guidelines. 12 months stability data has been provided. All of the data is within the stability specifications laid out in section 3.2.P.5.1 at all conditions. Therefore, the proposed storage conditions of "Do not store above 30 °C" are acceptable in line with the EMA guideline on the Declaration of storage conditions. The proposed shelf life of 24 months is also acceptable in line with ICH Q1E.

The stability studies on the pilot batch sizes can be considered representative of the commercial scale manufacture without further justification, as they are within 10 – fold of the largest commercial scale size and it is a standard manufacturing process.

The photostability study is acceptable and it is accepted that the drug product is not sensitive to light.

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Drug substance

Outstanding Major Objections remain on the control strategy proposed for potential impurities in the drug substance.

A number of Other Concerns also remain unresolved.

Drug product

The Major Objections raised at Day 80 on the drug product have been resolved.

Only two other concerns remain outstanding.

3.2. Non-clinical aspects

3.2.1. Introduction

The nonclinical development programme includes a full package of nonclinical studies in line with ICH M3(R2) guidance. Oteseconazole is referred to as VT-1161 throughout the nonclinical study reports. It was administered by oral gavage once daily to mimic the intended clinical route. The in-vitro and in-vivo mycology data (primary pharmacodynamics) are included in the clinical pharmacology section. The inhibitory activity and selectivity of oteseconazole for fungal CYP51 versus human CYP51 was evaluated in in-vitro pharmacology studies and oteseconazole was tested against a broad range of fungal clinical isolates including *Candida, Coccidioides, Cryptococcus* species and dermatophytes, including isolates with reduced susceptibility to azoles and echinocandins. Murine models of systemic infection were used to evaluate the potential of oteseconazole to reduce fungal burden and its benefit on survival. Oteseconazole was also evaluated in a guinea pig model as an oral treatment of dermatophytosis and in a murine model of vaginal candidiasis. The activity of oteseconazole towards other cytochrome P450 (CYP) enzymes, non-cytochrome metalloenzymes, and a broad panel of receptors, ion channels, and transporters was assessed as an early determination of potential off-target effects and drug-drug interactions. To address safety pharmacology endpoints the effects of oteseconazole on neuropharmacological and pulmonary systems were evaluated in male Sprague Dawley rats. In addition, the cardiovascular effects of oteseconazole were evaluated in an in-vitro assay for hERG activity and in telemetered male Beagle dogs.

Pharmacokinetic absorption and bioavailability studies with oteseconazole were conducted in rat and dog. The effect of food on oteseconazole absorption was evaluated in dog. In addition, toxicokinetic (TK) data were obtained as part of the mouse, rat and dog repeat-dose toxicology studies and in carcinogenicity studies and reproductive and developmental toxicology studies. Plasma protein binding has been evaluated *in vitro* with mouse, rat, dog and human plasma. Tissue distribution and excretion mass balance were assessed following administration of [^{14}C]oteseconazole to rats. In-vitro metabolism has been assessed in rat, dog and human primary hepatocytes. Inhibition and induction of human cytochrome P450 isozymes and human transporters has been assessed *in vitro*.

The toxicity profile of oteseconazole was evaluated in repeat-dose studies of up to 26 weeks in rats and up to 39 weeks in dogs, as well as in mouse and rat carcinogenicity studies. Oteseconazole, formulated as a suspension in 0.5% carboxymethylcellulose (CMC), was dosed by oral administration to mimic the clinical route. A standard panel of genotoxicity studies was conducted. In addition, the effects of oteseconazole on fertility, early embryonic development and embryo-fetal development were evaluated in rats and rabbits as well as in pre- and postnatal development studies in rats. Additionally, targeted pre- and postnatal development studies were conducted in rats to characterise effects on postnatal ocular development. In-vitro and in-vivo phototoxicity studies were also conducted.

3.2.2. Pharmacology

Oteseconazole is a novel, orally bioavailable selective inhibitor of fungal lanosterol demethylase (LD, CYP51). CYP51, an enzyme essential for fungal growth, catalyses an early step in the biosynthetic pathway of ergosterol, a sterol required for fungal cell membrane formation and integrity (Yosida, 1988). Inhibition of CYP51 results in the accumulation of 14-methylated sterols, some of which are toxic to the fungus. CYP51 is the molecular target of the class of drugs referred to as azole antifungals. All approved azole drugs contain either an imidazole or triazole ring system (Hitchcock, 1991) that binds tightly to the catalytic haem-iron of fungal CYP51 as well as to the haem-iron of many off-target mammalian cytochrome P450 enzymes. This inherent lack of selectivity is responsible for many of the

side effects associated with the azole antifungals. In contrast, oteseconazole has a lower affinity for haem-iron and a greater affinity for the fungal CYP51 polypeptide than do the current azole drugs (Hoekstra et al., 2014, Warrilow et al., 2014).

3.2.2.1. Primary pharmacodynamic studies

Osteseconazole demonstrated a high binding affinity for *C. albicans* CYP51 (CaCYP51) with a Kd of ≤39 nM. It was also shown to inhibit CaCYP51 with an IC50 of 1.5 µM, an effect equivalent to control azoles, fluconazole, itraconazole and voriconazole (IC50s 1.4 to 1.6 µM) but did not inhibit human CYP51 activity at drug concentrations up to 50 µM. Thus, oteseconazole demonstrated selectivity for the target fungal enzyme and minimal interaction with the human/host enzyme.

Oteseconazole was tested against a broad panel of fungal clinical isolates and showed activity against *Candida*, *Coccidioides* and *Cryptococcus* species as well as dermatophytes (most MIC values ranged from <0.015 to 0.25 µg/mL). Oteseconazole was active against clinical isolates with reduced susceptibility to azoles and echinocandins, with no to moderate increases in MICs. Oteseconazole was also active against endemic fungi.

In order to demonstrate selectivity for the target fungal CYP51, oteseconazole was tested against multiple other key mammalian P450 enzymes. Oteseconazole was shown to directly inhibit a number of human liver CYP enzymes. The inhibitory effect of oteseconazole on a number of CYP enzymes critical for steroid biosynthesis was also investigated. For CYP19, a key enzyme in the biosynthesis of oestrogens, the IC_{50} for oteseconazole was 7 µM, approximately 180-fold greater than the oteseconazole upper limit Kd value of <=39 nM for fungal CYP51.

The potential for oteseconazole to inhibit steroid biosynthesis was further investigated in a hamster model. The study demonstrated that oteseconazole did not significantly alter testosterone, progesterone or cortisol levels in male hamsters in a dose range of 10 to 50 mg/kg.

Oteseconazole showed antifungal activity in a murine model of vaginal candidiasis and retained activity *in vivo* when clinical isolates resistant to fluconazole were tested. Oteseconazole was also evaluated in a cutaneous candidiasis model in guinea pigs and showed equivalent or superior mycological outcomes and clinical scores to terbinafine and itraconazole. Furthermore, oteseconazole demonstrated antifungal activity in murine models of systemic infection with *C. albicans*, *C. glabrata*, and *C. neoformans* and showed clinical and mycological efficacy in a guinea pig model of dermatophytosis.

3.2.2.2. Secondary pharmacodynamic studies

Off-target effects of oteseconazole on non-cytochrome metalloenzymes and a broad panel of receptors, ion channels, and transporters were investigated. Oteseconazole was found to significantly inhibit metalloenzymes, endothelin converting enzyme (53%) and 5-lipoxegenase (97%), as well as human adenosine A3 receptor (93%), human melatonin MT1 receptor (81%), rat cerebral cortex Na^+ channel (site 2, 61%), rat cerebral cortex Cl^- channel (GABA-gated, 97%) human norepinephrine transporter (65%) and human dopamine transporter (71%). These findings were not considered clinically relevant due to the high protein binding of oteseconazole.

While below the significance criteria for the assay, inhibition of thromboxane synthase (36%) was observed in the metalloenzyme inhibition study, which may be indicative of weak to moderate effects. While incidences of haemorrhage were observed in developmental toxicology studies (Section 4.5 of

the nonclinical AR), these findings were not considered of clinical relevance due to high protein binding of oteseconazole and the absence of bleeding or haemorrhage findings in clinical studies.

3.2.2.3. Safety pharmacology programme

The effects of oteseconazole on the neurological and pulmonary systems were evaluated in male Sprague-Dawley rats. No apparent neuropharmacological or toxicological signs through 48 hours post-dose or any statistically significant changes in body temperature were observed at doses up to 1000 mg/kg, the highest dose studied. In the respiratory study, oral administration of oteseconazole at doses up to 1000 mg/kg did not produce any statistically significant changes in respiratory rate, tidal volume or minute volume. For both studies, the NOEL was determined to be ≥1000 mg/kg, the highest dose evaluated.

Oteseconazole inhibited the hERG potassium current with an estimated IC_{50} of 1.9 µM in human cells stably transformed to express the hERG channel. Based on an estimated clinical Cmax 2.7-3.6 µg/mL, and protein binding >99%, the free oteseconazole at clinically relevant exposures is calculated as ~50-fold lower than the hERG inhibitory concentration.

In a cardiovascular safety pharmacology study conducted in telemetered male beagle dogs, no oteseconazole-related changes in heart rate, systolic, diastolic and mean arterial blood pressure, cardiac rhythm or ECG morphology were noted at doses up to and including 300 mg/kg associated with a plasma concentration of 24,150 ± 6,881 ng/mL at 30 hours post-dose. The NOAEL for this study was ≥300 mg/kg, the highest dose evaluated, corresponding to an exposure margin of ~7-9 fold to the estimated clinical Cmax.

3.2.2.4. Pharmacodynamic drug interactions

Nonclinical pharmacodynamic interaction studies have not been performed.

3.2.3. Pharmacokinetics

Absorption

Oteseconazole pharmacokinetics are reported from three single dose PK studies in dogs. Oteseconazole was absorbed following oral administration, with peak plasma concentrations observed 24 hrs post-dose and a long terminal phase half-life in plasma (73.9 hr) (Study 0832DV22.001). In general, Cmax and AUC increased with increasing dose from 10 to 100 mg/kg (Study 0832DV22.001). However, a comparison of reported PK parameters in dogs between Study 0832DV22.001 and Study 0832DV22.002 at a 10 mg/kg oral dose demonstrates large differences between the two studies, calling into question the reliability of these data, due to the level of variability and low numbers included. Furthermore, the bioanalytical method used in both study 0832DV22.001 and Study 0832DV22.002 was an unvalidated LC/MS/MS method.

Reported PK values in study 0832DV00.002 are generally considerably lower than the equivalent measures in Study 0832DV22.001 at the same 10mg/kg dose level: Cmax (2.6-fold), Tmax (8-fold), t1/2 (2.1-fold), AUC (6.3-fold), CL (0.19-fold). Furthermore, the dose administered in study 0832DV22.001 was reported to be 8.8 mg/kg rather than the intended 10 mg/kg/day following dose-formulation analysis. Some sex-related differences in exposure in dogs are reported (Study 0832DV22.002), suggesting lower exposure in males compared to females at 10 and 30 mg/kg, although no difference is reported at 100 mg/kg. However, as only one dog is included in the study per sex per group, there are insufficient animals at each dose level to draw any conclusion on gender differences from this study. A food effect on the oral bioavailability of oteseconazole in dogs is also reported, based on the data from study 028823. The extent of absorption is reportedly different between the fed and fasted dogs following oral administration of 10 mg/kg oteseconazole (2.6 to 3.1-fold greater under the fed condition for Cmax and AUC). However, there is considerable inter-individual variability in the reported exposures in both the fed and fasted state, with some overlap between groups. Furthermore, the magnitude of the difference between the fed and fasted state is less than the unexplained difference in exposures reported between study 0832DV00.001 and study 0832DV00.002 (2.6-fold, 6.3-fold, for Cmax and AUC respectively).

Distribution

Plasma protein binding studies demonstrate that oteseconazole is highly protein bound, with rat plasma protein binding estimated to be approaching 100% (Study OPR-VMT-0086.01). In human plasma, oteseconazole protein binding was 99.8%, compared to >99.9%, 99.4% and 99.9% for itraconazole, posaconazole and ravuconazole, respectively (Study OPR-VMT-0449.014). Protein binding was also compared in mouse rat, dog and human plasma over a range of oteseconazole concentrations (260, 2500, 26,000, 105,000 ng/ml), with high protein binding in all species at all concentrations tested (Study MC11M-0008.01). Binding was slightly lower in mice (>96% vs. >99% in rat, dog and human) and slightly less at 105,000 ng/ml (93.7% in mice, ≥98.5% in rat, dog and human), suggesting possible saturation of binding at this high concentration.

Tissue distribution was assessed in a quantitative whole body autoradiography study conducted with [^{14}C]-oteseconazole, including both albino SD rats and partially pigmented Long Evans rats. In both albino and partially pigmented rats, [^{14}C]-oteseconazole-derived radioactivity was widely distributed with most tissue concentrations greater than blood concentrations by 1 hr post-dose.

No specific association of [^{14}C]oteseconazole-derived radioactivity with melanin is reported, based on radioactivity concentrations observed in melanin-containing tissues such as the eye uveal tract and pigmented skin. Although Cmax in most tissues (31 of 46 tissues) was reached by 24 hours post-dose

in partially pigmented rats, the tissues that reached Cmax at later time points included the eye lens (120 h) and hair/fur (96 h). However, the highest overall concentrations were observed in the contents of the alimentary canal, in stomach, large intestine, caecum and bile, which reflects the routes of elimination for oteseconazole and normal movement of the radioactive dosing material through the alimentary canal after an oral dose. Most tissue concentrations decreased 48 hours post-dose at a similar rate to elimination from the blood. However, elimination was not complete 1372 hours post-dose.

Placental transfer and excretion in milk were assessed from PPND studies in rats. Oteseconazole plasma concentrations were approximately 2-fold higher in F_1 pups compared to dams on PND 4 and remained elevated on PND 20. There was no consistent difference between the male and female pup concentrations on PND 20. Oteseconazole exposure in cross-fostered pups indicated F1 exposure was achieved both in utero and via milk transfer.

Metabolism

Oteseconazole was not significantly metabolised when incubated in vitro with mouse, rat, or human hepatocytes and little to no substrate loss was observed in the presence of various recombinant human CYP enzymes. Only one metabolite, consistent with hydroxylation and glucuronidation of oteseconazole, was detected in dog hepatocytes. Oteseconazole was not a substrate for any of the transporters tested, and the range of transporters studied is considered sufficient.

The molecular weight of oteseconazole is 527.4 g/mol and the clinical mean plasma oteseconazole at end of treatment (so reflecting accumulation with repeat dosing) was between ~2.7 µg/mL in CL-017 and ~3.6 µg/mL in CL-012. However, oteseconazole is >99% protein bound so the free fraction at end of treatment could be estimated at somewhere between 0.027-0.036 µg/mL. Therefore, in vitro enzyme and transporter interactions studies (some of which used up to 200 µM) used adequate drug concentrations.

Oteseconazole was found to be a direct inhibitor of CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4/5, CYP2C9 and CYP3A4/5 but there was little or no evidence for direct inhibition of CYP1A2. Oteseconazole did not appear to cause time-dependent or metabolism-dependent inhibition of any CYP enzyme examined. In studies of enzyme induction, treatment with up to 10 µM oteseconazole gave increases in CYP1A2, CYP2B6 and CYP3A activity as well as in CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 mRNA levels that were $\geq$ 2-fold compared to vehicle control and/or $\geq$20% of the positive control in at least two culture preparations. Except for CYP2C19 and CYP3A4 mRNA levels, 30 μM oteseconazole caused a decrease in or a loss of CYP activity, consistent with the morphological decline observed at this concentration. The applicant assessed the DDI liability related to CYP inhibition and induction by oteseconazole using basic and mechanistic static models in accordance with FDA guidance. The FDA guidance is not fully aligned with the EMA Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**), which is applicable to this submission. Nevertheless, the applicant's conclusion (i.e. that there is negligible risk of clinically significant DDIs with the CYP isoforms evaluated in vitro ADME studies with oteseconazole and that in vivo studies are not recommended) can be agreed. It is noted that a clinical study was conducted with midazolam (see clinical AR).

Oteseconazole inhibited human transporters P-gp, BCRP, OATP1B1, OATPB3, MATE1 and MATE2-K in vitro. No significant inhibition of OAT1, OAT3, and OCT2, ASBT, NTCP, or MRP2-mediated transport at up to 10 µM, but oteseconazole did inhibit BSEP-mediated transport. Based on the physicochemical properties (e.g. neutral charge, low aqueous solubility) and the high degree of protein binding of oteseconazole, the risk of clinically relevant transporter inhibition was assessed as low for all of the transporters assessed, with the exception of BCRP. A clinical DDI study was performed using

rosuvastatin as a sensitive substrate of BCRP and is described in the clinical AR (Section 2.19 – Interactions).

Elimination

The primary route of elimination of radioactivity after oral [^{14}C]-oteseconazole dosing was in the faeces, which accounted for an average of 82.8% of the administered dose. An average of 0.7% of the administered dose was recovered in the urine. Excretion of radioactivity in faeces was prolonged; 25.5% of the administered dose was eliminated in the initial 24 hours post-dose and recovery continued through 504 hours post-dose.

3.2.4. Toxicology

3.2.4.1. Single dose toxicity

In a single dose study in rats, a NOAEL of > 1000mg/kg was reported, i.e. > the highest dose tested in this study (Study 025745). However, delayed absorption was reported at the 300 mg/kg and 1000 mg/kg dose levels and plasma concentrations at 1000mg/kg were not further increased compared to the 300 mg/kg dose level. Therefore, maximal exposure was achieved at 300 mg/kg/day, with an expectation of accumulation with multiple dosing also suggested. Furthermore, changes in epididymis and testes organ weight were reported in the study and variability in clinical pathology measures were also seen, although these findings were not considered adverse under the conditions of the study.

An MTD was not defined in a dose range finding study in dogs with single oral doses of up to 300mg (males)/ 1000 mg/kg (females) tolerated (Study 0406DV22.001). Clinical signs of emesis, soft faeces and a reduction in food consumption in males were reported but were not considered adverse. Similar to the rat study, absorption was delayed at the higher doses in dogs, with Tmax reported at 2-4 hours in the 30 mg/kg dose group and at 24hrs in the higher dose groups. Exposure was maximal in the 300 mg/kg group, with a lower exposure reported at 1000 mg/kg than at 300 mg/kg. Of note, a very long half-life was reported (187 to 512 hours) at all dose levels.

3.2.4.2. Repeat dose toxicity

Mice

In an acute repeat-dose study, oral dosing was for 5 days with up to 300 mg/kg once daily oteseconazole to CByB6F1 non-transgenic wild-type mice. A MTD of 100 mg/kg/day was defined, due to mortality in the high dose group (Study 2130-021).

In the pivotal GLP-compliant repeat-dose study in CByB6F1 non-transgenic wild-type mice, once-daily oral doses of 0, 5, 15 and 50 mg/kg/day oteseconazole were administered for 28 days (Study 2130-022) with TK evaluation on Days 1 and 28 (days 1 and 17 for the high dose group). All animals dosed orally by gavage with oteseconazole were exposed to the test article. There were no apparent sex differences in oteseconazole exposure (<2-fold). Dose-related increases in Cmax and AUC_{0-24} were approximately proportional from 5 to 15 mg/kg/day. Oteseconazole accumulation tended to increase with each increase in dose, although the high dose group was assessed 11 days earlier than the low and mid dose groups, as the high dose of 50 mg/kg/day was not tolerated. Fourteen animals were euthanised *in extremis* between days 13 and 17 due to poor clinical condition at 50 mg/kg/day. Adverse clinical signs without associated microscopic findings and adverse body weight effects were

also noted in both sexes at 50 mg/kg/day. No test article-related effects were noted in clinical or veterinary observations, body weight, body weight change or food consumption at 5 or 15 mg/kg/day.

At ≥5mg/kg/day mild to moderate increases is AST, ALT, ALP with corresponding microscopic findings in the liver were reported, including hepatocellular vacuolation, hypertrophy and/or necrosis and increased liver weights. The hepatocellular effect was considered adverse in both sexes at ≥15 mg/kg/dose based on the collective severity of ALT and AST increases and microscopic findings in the liver. Inflammatory changes were also present, with increased lymphocyte and monocyte counts in females at 15 mg/kg/day and increase globulin concentration in both sexes at ≥5 mg/kg/day. Decreased reticulocyte count in both sexes at ≥5 mg/kg/day was reported associated with decreased mean corpuscular volume (MCV) and mean corpuscular haemoglobin (MCH), reflecting decreased erythropoiesis. Signs of altered lipid metabolism were present at ≥ 5 mg/kg/day, with increase triglycerides and cholesterol, decreased glucose concentration in males and decreased potassium and chloride concentrations in both sexes.

Other anatomic pathology effects reported at ≥5 mg/kg/day include adrenal cortical vacuolation associated with increased adrenal weights. In females at ≥5 mg/kg/day, absent corpora lutea were noted in the ovaries, while at 50 mg/kg/day thin vaginal epithelium, reduced uterine size, and absent ovarian corpora lutea were reported, consistent with reproductive immaturity. Decreased uterine weights at 50 mg/kg (-70.3% - -73.9%) had no microscopic correlates. In males, reduced luminal sperm in the epididymides was noted at ≥5 mg/kg/day, with increased germ cell debris at 50 mg/kg/day and associated decreased epididymal weights at all dose levels (-5.3% to -28.5%). Decreased prostate weights were reported at ≥5 mg/kg/day (-44.7% - -72.9%) without microscopic correlates.

These findings were not considered adverse, hence the NOAEL in males and females is reported as 5 mg/kg/day, which is associated with a Day 28 AUC_{last} of 246,000 h*ng/mL and a Cmax of 12,600 ng/mL. A high dose of 5 mg/kg oteseconazole in males and 15 mg/kg/day in females was selected for the 6-month carcinogenicity study.

Rats

In an acute repeat-dose study in rats, once-daily oral doses of up to 300 mg/kg oteseconazole were administered for 7 days (Study 025949). Mortality was observed in the two highest doses of 100 mg/kg and 300 mg/kg. A NOAEL was not defined due to increased liver weights reported at the lowest dose tested of 30 mg/kg/day, with associated microscopic findings of mild diffuse hepatocellular hypertrophy and multifocal vacuolation of midzonal hepatocytes. Day 7 Cmax and AUC_{2-24} values were 4.8- to 9.4-fold greater than the corresponding Day 1 values, indicating accumulation of oteseconazole in the plasma compartment over the course of this 7-day study. A second acute study in SD rats was conducted to further explore findings reported in male reproductive organs, including microscopic findings in the epididymes and testes and decreased prostate weights at ≥100 mg/kg/day. As in the first study, there was once-daily oral dosing of 30 and 100 mg/kg/day oteseconazole for 7 days, although the high dose of 300 mg/kg was not included due to the mortality previously observed at this dose level (Study 2130-019). A NOEL for effects on the male reproductive system at 30 mg/kg/day based on organ weights, histopathology and serum hormone data is reported. However, serum hormone changes were also present in the 30 mg/kg/day dose group. Hormonal analysis showed, at 100 mg/kg/day, moderate decreased in mean serum 17α-hydroxyprogesterone, androstenedione, testosterone and dihydrotestosterone concentrations, and a compensatory mild increase in mean luteinizing hormone and progesterone concentrations. Mean serum follicle stimulating hormone concentration was also mildly increased. In the 30 mg/kg/day dose group, mean 17OH-progesterone, testosterone and dihydrotestosterone concentrations were also mildly decreased, without apparent

increases in LH concentration. These effects on male reproductive organs and sperm parameters in rats are considered secondary to decreased androgen tone and in the absence of an effect on circulating hormones in human males (study VMT-VT-1161-CL-005) are likely to represent a minimal risk for potential effects in humans.

In a pivotal, GLP-compliant repeat-dose toxicity study in SD rats, once daily oral doses of 0, 5, 25, 60 and 120 mg/kg/day oteseconazole were administered for 28 days (Study 0436RV22.003) with a 42-day recovery period. The two highest doses of 60 and 120 mg/kg/day were not tolerated, with mortality observed at both dose levels, including the unscheduled deaths of all rats in the 120 mg/kg/day group on Day 11. The unscheduled death of one male in the 25 mg/kg TK group is also reported. Clinical signs observed at ≥60 mg/kg/day included red staining of the nares and around the mouth, decreased activity and abnormal stance and gait, hunched posture, ruffled hair coat, decreased or no righting reflex, lethargy, prostrate, cool to touch, no activity, hypersensitivity to touch, vocalization, ataxia, falling over in cage when trying to move and/or seizure. Decrease body weight was also reported at ≥60 mg/kg/day. A NOAEL was not identified in this 28-day study due to adverse findings of hepatocellular hypertrophy and necrosis, adrenocortical vacuolation and alveolar histiocytosis at the low dose of 5 mg/kg/day.

A subsequent **14-day** GLP-compliant study was conducted in SD rats, with once daily oral doses of 0, 1, 3 and 5 mg/kg/day oteseconazole (Study 0437RV22.001) with a 14-day recovery period. All animals survived until scheduled necropsy (on day 15 or day 29 for recovery animals). No test-article related clinical signs and no effects on body weight or food consumption were reported. Test article-related haematological findings of increased platelet counts were reported at 5 mg/kg/day and lower prothrombin times in females dosed with 3 and 5 mg/kg/day were not considered adverse. Clinical chemistry findings included increased mean globulin values at all dose levels. Related increased total protein values at all dose levels and lower albumin/ globulin (A/G) ratios in the 3 and 5mg/kg dose groups were also reported. These findings were reported as test-article related and did not resolve in the 5 mg/kg/day dose group. Globulin and/or total protein differences were more pronounced following the recovery period but were not considered adverse due to the magnitude of change and lack of inflammation. Elevated calcium levels in males at all dose levels was considered secondary to higher globulin and total protein levels, although there was no dose-response and calcium remained elevated in males given 5 mg/kg/day following recovery. A NOAEL of 3 mg/kg/day was reported due to findings of liver hypertrophy (with coagulative necrosis), adrenocortical vacuolation, and pulmonary alveolar histiocytosis at 5mg/kg/day, which is consistent with the 28-day study.

In the pivotal GLP-compliant chronic study in SD rats, once daily oral doses of 0, 0.15, 0.5, 1.5 and 5 mg/kg/day oteseconazole were administered for **26 weeks** (Study 2130-002), The main test article related effects reported include reversible minimal to mild hepatic subcapsular necrosis and minimal focal hepatic necrosis in males at 5 mg/kg/day, minimal hepatic single cell necrosis in both sexes at 5 mg/kg/day and microscopic lesions in the kidney consisting of exacerbation of bilateral chronic progressive nephropathy (CPN) in both sexes at 1.5 and 5 mg/kg/day. The increase in the CPN correlated to increased proteinuria observed in rats at these two dose levels.
Based on these findings it was concluded that the NOAEL for oteseconazole was 0.5 mg/kg/day, corresponding with a Cmax of 667 ng/mL and AUC_T of 14,500 ng·hr/mL at Week 26.

Dogs

In an acute repeat dose study in beagle dogs, once-daily oral dosing of up to 300mg/kg/day was well tolerated for 7 days. A NOAEL of 300 mg/kg/day was reported, associated with a day 7 Cmax = 104,000 ng/ml and 43,100 ng/ml in males and females respectively (n=1/ group), with AUC_{0-24} = 2,240,000 ng·hr/mL and 944,000 ng·hr/mL, respectively.

In the pivotal GLP-compliant 28-day repeat-dose study in dogs, daily oral dosing of 0, 10, 30 and 100 mg/kg/day oteseconazole was administered (Study 0040DV22.004). There was blood sampling pre-dose (0hr) and 2-, 4-, 8-, 12-, 16-, 20- and 24-hours post-dose on days 1, 14 and 28 for TK analysis. Mortality occurred at the high dose with a single female sacrificed on Day 21 with adverse clinical signs.

Clinical signs at 100 mg/kg/day included thin body condition, whole body tremors, excessive licking at sides of mouth, excessive head shaking, abnormal stance and gait, hunched posture and inability to stand. At recovery, clinical signs were no longer present with the exception of thin body condition and hunched posture in a single female at 30 mg/kg/day and excessive head shaking and hunched posture in a single female at 100 mg/kg/day. Decreased body weight relative to control animals was observed in females at 100 mg/kg/day, which persisted during the recovery period; changes in body weight correlated with decreased food consumption. Additionally, decreased body weight relative to controls was observed at 30 mg/kg/day during the recovery period only. There were treatment-related effects on clinical chemistry parameters on Day 29, including an increase in cholesterol levels at 100 mg/kg/day, which was reversed during the recovery phase.

Findings in the mandibular and mesenteric lymph nodes, ileum (Peyer's patches) and spleen were observed at ≥30 mg/kg/day, including minimal to moderate increase of body macrophages predominantly in the germinal centres of mandibular and mesenteric lymph nodes and in the Peyer's patches of the ileum. In addition, minimal to slight lymphoid depletion occurred in the mandibular and mesenteric lymph nodes of dogs from all oteseconazole-treated groups, but without a clear dose relationship so the relationship to oteseconazole treatment was considered uncertain. Also, oteseconazole at 100 mg/kg/day caused a minimal increase of body macrophages in the splenic germinal centres in one male dog. At the end of the recovery period, all oteseconazole-related findings in the mandibular and mesenteric lymph node and spleen were reversed. Tingible body macrophages were still minimally increased in the ileum Peyer's patches of 1 female previously dosed at 30 mg/kg/day. The NOAEL was reported as 10 mg/kg/day, associated with Day 28 Cmax and AUC_{0-24} values of 25,900 ng/mL and 547,933 ng·hr/mL, respectively.

In the pivotal GLP-compliant chronic study in dogs a loading dose of 0, 0.75, 2.5, 7.5 or 20 mg/kg/day oteseconazole was administered for 5 weeks, followed by maintenance dosing of 0, 0.75, 1.5, 5.5 or 17mg/kg/day oteseconazole, for a total treatment duration of **39 weeks** (Study 2130-001), with blood sampling on days 1, 14, 111 and 273 for TK analysis. Dogs were evaluated for mortality, clinical signs, body weight, food consumption, ophthalmoscopy, ECG, clinical pathology, and anatomic pathology.

A decrease in body weight was observed at 17 mg/kg/day compared to controls. Mean body weight in the 17 mg/kg/day females was consistently lower than controls throughout the study. The decrease was considered oteseconazole-related, but non-adverse since the mean was not more than 10% lower than controls. Macroscopic observations included enlarged adrenal glands in two females at 17 mg/kg/day that were considered oteseconazole-related and correlated microscopically to hypertrophy/hyperplasia of adrenal gland cortex. Additionally, there were statistically significant increases in mean adrenal weights in males at 5.5 mg/kg/day and in males and females at 17 mg/kg/day when compared to controls. Increased adrenal gland weights correlated microscopically to hypertrophy/hyperplasia of adrenal gland cortex which was moderate to severe. The microscopic

changes consisted of either enlarged and/or increased numbers of cortical cells in the zona fasciculata area of adrenal cortex. In addition, increased vacuolation of zona fasciculate cortical cells was observed at ≥1.5 mg/kg/day and mononuclear cell infiltration was observed at ≥0.75 mg/kg/day. These changes were considered oteseconazole-related but were not associated with necrosis, disruption of glandular architecture, or clinical pathology findings and therefore, were not considered adverse. TEM evaluation of the zona fasciculate disclosed lipid vacuoles that were considered increased in one or more images from the male and female dogs at 17 mg/kg/day. The proportion of lipid vacuoles to mitochondria and smooth endoplasmic reticulum was considered increased in the cytoplasm of the affected cells. There were statistically significant decreases in mean prostate gland weights in terminal males at 17 mg/kg/day when compared to controls (51% for absolute weights). The decreased prostate gland weights at 17 mg/kg/day were considered test article-related but not adverse since all glands were within normal limits microscopically. All the above findings resolved during the 33-week recovery period.

Based on these results, a NOAEL at the high dose of 17 mg/kg/day is reported corresponding with Day 273 mean Cmax of 74,700 ng/mL and AUC_{0-24} of 1,675,000 ng· hr/mL (≈30- and 23-fold safety margin relative to anticipated human exposure at the MRHD for acute VVC and RVVC, respectively, based upon an AUC comparison). Although findings of increased adrenal weights with moderate to severe hypertrophy/ hyperplasia of the adrenal gland cortex and vacuolation of the *zona fasiculata* and significantly decreased prostate gland weights at 17mg/kg/day are reported, all findings were reversible during the recovery period.

3.2.4.3. Genotoxicity

Oteseconazole was found to be negative in a standard battery of GLP-complaint genotoxicity tests, in line with ICH S2(R1), including a bacterial reverse mutation assay, an in vitro chromosome aberrations assay in human peripheral lymphocytes and an in vivo bone marrow micronucleus assay in rats.

3.2.4.4. Carcinogenicity

In a GLP-compliant 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic[rash] Transgenic mice (Study 2130-025), once daily oral dosing of up to 5mg/kg oteseconazole in males and up to 15mg/kg/day oteseconazole in females was administered daily for 26 weeks. A positive control group was also included in which 75mg/kg/day N-Nitroso-N-methylurea (NMU) was administered daily. No test article-related clinical or veterinary observations were noted and there was no test article-related effect on mean body weight, mean body weight gain, or mean food consumption. Additional satellite animals were treated with oteseconazole for TK evaluation. All animals dosed orally by gavage with oteseconazole were systemically exposed to the test article. Where applicable, there were no apparent sex differences in oteseconazole exposure. Administration of oteseconazole at oral doses ranging from 0.5 to 5 mg/kg/day in males and 1.5 to 15 mg/kg/day in females produced a greater than proportional increase in plasma VT-1161 concentrations on Days 28 and 182.

There was no test article-related carcinogenicity reported. Early deaths noted in the study were considered the result of spontaneous or incidental tumours, incidental non-neoplastic lesions or undetermined causes. The tumours noted had low incidence, lacked a dose-dependent increase in incidence, and fell within the historical control range. Test article-related non-neoplastic findings were present in the liver of males and females, adrenal gland of males and females, ovaries of females, and mammary glands of females, consistent with toxicity findings in the repeat-dose studies in mice, with the possible exception of the mammary gland atrophy.

Based on the available data, it was concluded that oteseconazole was well-tolerated for 26-weeks and did not produce any evidence of a carcinogenic effect on the CByB6F1-Tg(HRAS)2Jic Hemizygous [rasH2] transgenic mouse model system at up to 5 mg/kg/day in males (AUClast = 246,000 ng·hr/mL) and up to 15 mg/kg/day in females (AUClast = 828,000 ng·hr/mL);with a reported ≈17- and ≈12-fold safety margin in females relative to anticipated human exposure at the MRHD for acute VVC and RVVC, respectively, based upon an AUC comparison.

In a GLP-compliant long-term carcinogenicity study in SD rats (Study 2130-018), with an intended duration of 104-weeks, once daily oral dosing of up to a high dose of 5 mg/kg/day oteseconazole (reduced to 3 mg/kg/day during the study) was administered for a maximum of 91 weeks due to a high incidence of mortality in all oteseconazole-treated groups. Additional satellite animals were treated with oteseconazole for TK evaluation and all animals were systemically exposed to the test article. Oteseconazole at oral doses ranging from 0.5 to 5 mg/kg/day in males and females produced a greater than proportional increase in plasma oteseconazole concentrations with effects more pronounced in females. Oteseconazole concentrations appear to be higher in females compared to males; this gender related increase in plasma concentrations is most prominent at 5/3 mg/kg/day.

The following parameters and endpoints were evaluated in this study: mortality, clinical observations, masses, body weight, and food consumption, toxicokinetic parameters, gross necropsy findings, and histopathologic examinations. The applicant reports that all clinical signs and masses observed were consistent with the expected reference ranges for carcinogenicity studies based on the historical control data in males and female rats of this age and strain at this test facility. Dose-related decreases in body weight were observed in males at all dose levels and females at 1.5 and 5/3 mg/kg/day. Generally, food consumption was decreased in males at 5/3 mg/kg/day during the first two months of dosing but was increased in males at all doses starting at 6 months and in females at all dose levels periodically throughout the study.

Oteseconazole-related unscheduled deaths occurred due to liver necrosis or multifocal haemorrhage (adrenal gland, brain, spinal cord, male reproductive tract, thoracic cavity, pancreas, thymus, and/or urinary bladder) in males at 5/3 mg/kg/day. Oteseconazole-related macroscopic findings of unilateral or bilateral thyroid gland enlarged, nodule, or mass were observed in both sexes at ≥ 1.5 mg/kg/day and frequently correlated with follicular cell hyperplasia, benign follicular cell adenoma, and/or malignant follicular cell carcinoma.

Non-neoplastic oteseconazole-related effects are reported in the thyroid gland, testes, liver, kidney, ovary, adrenal gland, and pancreas as follows: Minimal to moderate follicular cell hyperplasia in the thyroid gland in both sexes at ≥ 1.5 mg/kg/day; Dose-related increased incidence of minimal to moderate Leydig cell hyperplasia in the testes at ≥ 0.5 mg/kg/day compared to controls; Increased incidence of panlobular hepatocellular hypertrophy and multinucleated hepatocytes in both sexes at 5/3 mg/kg/day; Increased brown pigment (hemosiderin) in the liver and kidney of female at ≥ 1.5 mg/kg/day; Dose-related increased incidence of minimal to moderate vacuolation of the interstitial cells in the ovary at ≥ 0.5 mg/kg/day compared to controls; Dose-related increased of vacuolation of the adrenal cortical cells in males (minimal to marked) at ≥ 0.5 mg/kg/day and in females (minimal to moderate) at 5/3 mg/kg/day; Dose-related increased incidence of minimal to mild acinar cell vacuolation in the pancreas of females only at ≥ 1.5 mg/kg/day. Non-dose-dependent increased incidence and severity of chronic progressive nephropathy (CPN) in males at ≥ 0.5 mg/kg/day and in females at ≥ 1.5 mg/kg/day.

Neoplastic oteseconazole-related effects are reported in the thyroid gland, liver, testes, and uterus as follows: Benign follicular cell adenoma in the thyroid gland of both sexes at ≥ 1.5 mg/kg/day; Malignant follicular cell carcinoma in the thyroid gland in males at ≥ 1.5 mg/kg/day and in females at 5/3 mg/kg/day; Benign hepatocellular adenomas in males at ≥ 0.5 mg/kg/day; Malignant

hepatocellular carcinomas in females at 5/3 mg/kg/day; Benign Leydig cell adenoma in the testes at ≥ 1.5 mg/kg/day; Benign granular cell tumour in the uterus at 5/3 mg/kg/day. No unscheduled deaths directly attributed to oteseconazole-related neoplastic findings are reported. This tumour development in rats following chronic treatment with oteseconazole, is reported as secondary to hepatic microsomal enzyme induction (thyroid and liver tumours) and increased concentrations of luteinizing hormone (Leydig cell tumours) and considered the result of species-specific mechanisms in the rat, which is supported by the absence of tumorigenic findings in the Tg mouse carcinogenicity study. However, the possible clinical relevance of the uterine granular cell tumours cannot be excluded, on the basis of the available data.

3.2.4.5. Reproductive and developmental toxicity

DART studies characterising adverse effects of oteseconazole on mammalian reproduction were conducted in line with ICH S5(R3), including the following GLP compliant pivotal studies; fertility and early embryonic development (FEED) studies in males and females, embryo foetal development (EFD) studies in two species, rats and rabbits; and a pre- and post-natal development (PPND) study in rats. Four additional PPND studies were also conducted in SD and HAN Wistar rats, with the aim of further characterising the ocular toxicity findings in the F_1 generation from oteseconazole-treated dams identified in pivotal PPND study in SD rats.

In the GLP-compliant male FEED study (Study 2130-009) once daily oral doses of up to 10mg/kg were administered for 76 days, beginning 42 days prior to pairing with untreated females. Reproductive and fertility indices (mating [number mated and number of days to mating], fertility and fecundity) were unaffected after 42 days of treatment at all dose levels, and no effects are reported on reproductive outcomes in the mated females (pre- and post-implantation loss, numbers of implantation sites, viable fetuses, and resorptions) at any dose level. Changes in sperm motility and morphology are reported at ≥ 3mg/kg/day but the changes were considered non-adverse at 3mg/kg/day due to the magnitude of change and the lack of effect on reproductive and fertility indices. Hence, a NOAEL for sperm parameters is reported as 3 mg/kg/day (Cmax = 5,520 ng/mL; AUC_T = 118,000 ng·hr/mL). Test article-related macroscopic findings on the liver and decreased body weight gain at ≥ 3mg/kg/day was also considered non-adverse due to the magnitude of change. A NOAEL for general toxicity, including histopathology of reproductive organs, and for reproductive and fertility parameters is reported as 10 mg/kg/day (Cmax = 27,800 ng/mL; AUC_T = 604,000 ng·hr/mL).

In the GLP-compliant female FEED study (Study 2130-008) once daily oral doses of up to 25mg/kg/day were administered from 28 days prior to cohabitation with untreated males, throughout mating until gestational day (GD) 7. The applicant reports test-article related decreased fertility and fecundity indices (76% vs 96% in controls), increased post-implantation losses (9.37% versus 3.71% in controls) and increased mean number of resorptions (1.3 vs 0.5) at 25mg/kg/day, which were statistically significant from controls but within the range of historical control data. A slightly lower number of viable foetuses is also reported at 25mg/kg/day but not statistically significant from controls. Based on these data, the NOAEL for reproductive and fertility parameters in females was reported as 5 mg/kg/day. However, due to decreased mean body weight gain (-87% and -94%) at 5 and 25 mg/kg/day respectively, the NOAEL for general toxicity in females was reported as 1.5 mg/kg/day. Findings of increased liver weights with associated macroscopic findings (tan discoloration/ foci) were also reported at 1.5 mg/kg/day but were not considered adverse. The applicant reports Cmax and AUC values at the NOAEL for reproductive toxicity and fertility parameters based on PK data from the 28-day rat repeat dose toxicity study (Study 0436RV22.003 5mg/kg/day: Cmax = 12,835ng/ml, AUC_{0-24} = 233,340 ng·hr/mL), and extrapolated from this same study to the general toxicity NOAEL assuming pharmacokinetic linearity (1.5mg/kg/day: Cmax = 4,277 ng/ml, AUC_{0-24} = 77,780 ng·hr/mL).

In the GLP-compliant pivotal EFD study in SD rats a high dose of 40mg/kg/day was administered, dosed from GD 6 to GD17 *(*Study 2130-005). Test-article-related maternal toxicity is reported at 40mg/kg/day, with lower gestational body weight, reduced body weight gain and reduced food consumption during the treatment period. Based on these data, a NOAEL for maternal toxicity of 10mg/kg/day is reported (GD17: Cmax = 11,200 ng/ml, AUC_{τ} = 254,000 ng·hr/mL). However, there was no evidence of teratogenicity of the test article reported and a NOAEL at the high dose of 40mg/kg/day is reported for developmental toxicity (GD17: Cmax = 38,800 ng/ml, AUC_{τ} = 885,000 ng·hr/mL). Of note, there is evidence of significant accumulation across the dosing period due to the long half-life of oteseconazole in rats, with accumulation ratios ranging from 7.91 to 9.41, based on AUC on GD17 versus GD6.

In the GLP-compliant pivotal EFD study in rabbits, dosing up to 15mg/kg/day was administered from GD7 to GD 19 (Study 2103-007). At 15mg/kg/day 4/20 animals aborted and 1 animal delivered early, these animals were euthanized prior to scheduled termination on GD29. Maternal toxicity was evident at 15mg/kg/day, with adverse clinical findings (decreased activity, absent/few faeces, red material in pan, and thin appearance), significant weight loss, lower body weight gain and reduced food consumption. Mean foetal body weights were also significantly lower at 15mg/kg/day (-12%), although no test-article related teratogenic effects were noted. Based on these data the NOAEL for maternal and developmental toxicity was reported at 5mg/kg/day (GD19: Cmax = 5,980 ng/mL, AUC_{τ} = 137,000 ng·hr/mL), although absent/ few faeces (n≤5), thin appearance (n=2) and red material in pan (n=1) were also reported at ≥2mg/kg/day. These findings were not considered by the applicant to be adverse due to the transient nature or low incidence at the 2 and 5mg/kg/day dose levels. Significant accumulation was also noted in this study, with accumulation ratios based on AUC_{τ} values on GD 19 versus GD 7, ranging from 7.71 to 12.4.

In a dose range finding pre- and post-natal development (PPND) study in SD rats, dosing up to 20mg/kg/day was administered from GD 6 to lactation day (LD) 20 (Study 2130-026). Maternal body weights and body weight change were significantly lower at 20 mg/kg/day, with lower mean food consumption was observed during gestation and throughout lactation at 10 and 20 mg/kg/day correlating with decreased pup body weights. Excessive pup mortality and marked decreases in pup growth were also reported at 20 mg/kg/day, and at ≥10mg/kg/day a lower number of total pups/litter at birth and liveborn pups/litter at birth is also reported.

In the GLP-compliant pivotal PPND study in SD rats, dosing up to 7.5 mg/kg/day was administered to female [Crl: CD(SD)] rats from GD6 to LD20 (Study 01234001). No test article-related effect on dams is reported with oteseconazole treatment up to 7.5mg/kg/day. In the offspring, test-article related toxicity was observed in the 7.5mg/kg/day group, with lower mean body weight gain reported in F_1 pups of treated dams. Adverse, treatment-related ocular toxicity was also observed in the 7.5 mg/kg/day group, with unilateral exophthalmos and/or eye opacity observed. Based on these data, the NOAEL for maternal toxicity and effects on gestation, parturition and lactation was 7.5 mg/kg/day (GD 18: Cmax = 14,200 ng/mL, AUC_{0-24} = 297,000 ng·hr/mL; LD 20: Cmax = 4,780 ng/mL, AUC_{0-24} = 97,500 ng·hr/mL). However, in the F_1 offspring, the NOAEL was reported at 3 mg/kg/day for F_1 growth and eye development (GD 18 Cmax = 6430 ng/mL, AUC_{0-24} = 129,000 ng·hr/mL; LD 20: Cmax = 1510 ng/mL, AUC0-24 = 30,500 ng·hr/mL), with a NOAEL of 7.5 mg/kg/day for F_1 reproductive function and neurobehavior. Pup plasma levels were 2- to 5-fold greater than maternal plasma levels at all doses through PND 20, and measurable through PND 35 at 7.5 mg/kg/day. Additionally, some F_1 mortality is reported, although this mortality was not considered treatment-related as it did not demonstrate a clear dose-response.

In the GLP-compliant first investigational PPND study in SD rats, 0 or 7.5 mg/kg/day oteseconazole was administered to female [Crl: CD(SD)] rats from GD6 to LD20 (Study 01234002), with ophthalmology evaluations beginning after eye opening until at least PND50. Consistent with the previous pivotal study, no test article-related effects on dams were reported but treatment-related toxicity was reported in F_1 pups, including decreased body weight gain and ocular toxicity, with exophthalamus (with or without discoloration) observed. Clinical observations from ophthalmic examinations included opacity, increased incidence of cataracts, vitreous haemorrhage, anterior lens luxations, and hyphema progressing to phythisis bulbi, all of which were considered test-article related. Furthermore, haematological findings are also reported in F_1 pups, including decreased erythrocyte mass, increased reticulocyte count (Females only), together with gross and microscopic findings of haemorrhage of the dorsal thoracic region of the skin, at the site of microchip implantation. At necropsy, lens degeneration was noted at higher incidence in test article-exposed animals and the related finding of cataract was noted at higher incidences in test article-exposed animals by ophthalmological exam, with increased incidence over time. Lower brain weights (approximately 5%) were also noted at the scheduled necropsy on PND 61-62. Of note, significant post-weaning mortality occurred in F_1 generation pups (n=84 deaths), attributed to excessive haemorrhage following sub-cutaneous microchip implantation on PND21.

In a second investigational PPND study in SD rats, 0 or 7.5 mg/kg/day oteseconazole was administered to female [Crl: CD(SD)] rats from GD6 to LD20 (Study 01234003). Consistent with the previous pivotal study, no test article-related effects on dams were reported. Test-article related mortality in the F_1 generation was reported pre-weaning (n=6 pups) and post-weaning (n=5 pups) following identification procedures at the time of weaning, but there was no apparent difference in the incidence of mortality following microchip versus ear tag identification, and the incidence of mortality was markedly lower than in the previous study. Ocular toxicity was also reported, including cataracts, intraocular haemorrhage, lens degeneration and optic nerve atrophy. Altered red cell and coagulation parameters are also reported.

In the third investigational PPND study in SD and Han Wistar rats, 0 or 7.5 mg/kg/day oteseconazole was administered to female [Hsd: CD(SD)] and female Crl:WI(Han) rats from GD6 to LD20 (Study 01234004). Consistent with the previous PPND studies, no test article-related effects were reported on dams with the exception of increased mean body weight gains, noted in both strains during lactation. This treatment-related effect, resulting in higher mean body weights in these groups vs their respective control groups, was not considered adverse. Although paradoxically, mean food consumption in the 7.5 mg/kg/day SD group was lower compared to the SD control group during the lactation dosing period. Treatment-related mortality in F_1 generation was reported pre-weaning (n=2 SD pups) and post-weaning (n=1 SD + n=1 HAN). Test-article related findings of tremors and swollen abdomen were common to F_1 pups of both strains, and findings of swollen abdomen continued throughout the post-weaning period. Additionally, adverse treatment-related findings of sub-cutaneous haemorrhage, pale eyes, lower mean body weight and body weight gain, were reported in the offspring of oteseconazole-treated SD rats. Mortality in the HAN offspring was associated with soft eyes and opacity in both eyes. Ocular toxicity, including enophthalmus and dark red discoloration were noted in F_1 SD rats, with exophthalmus reported in the F_1 HAN group. While these eye findings were observed at low incidence in these groups, they were considered test article-related based on similarity to findings observed for previous studies. Treatment-related cataracts were also observed in F_1 pups from both rat strains. Alterations in hematology, coagulation, and serum chemistry parameters were also noted in F_1 generation animals, with higher severity in the SD rats.

In the GLP-compliant cross fostering PPND study in SD rats, 0 or 7.5 mg/kg/day oteseconazole was administered to female [Hsd: CD(SD)] from GD6 to LD20 (Study 8475242). In Group 1, dams were administered 0 mg/kg/day and pups were not-cross fostered. Group 2 dams were also administered 0

mg/kg/day but pups were cross-fostered to group 3 dams. Group 3 dams were administered 7.5mg/kg/day oteseconazole and pups were cross-fostered to group 2 dams. Group 4 dams were administered 7.5mg/kg/day oteseconazole and pups were not cross-fostered. No treatment-related effect on dams was reported with the exception of non-adverse clinical observations of vocalization noted for F_0 animals during gestation. In F_1 pups an oteseconazole-related, non-adverse increase in absent visceral variation innominate artery was noted. However, no effect of oteseconazole exposure or cross-fostering was noted on F_1 survival, clinical observations, body weight, ophthalmic observations, or macroscopic observations. Hence, in contrast to findings from the previous study in Hsd:SD rats, a no observed adverse effect level is reported at 7.5 mg/kg/day for this study.

3.2.4.6. Toxicokinetic data

TK analyses conducted for the pivotal GLP-compliant repeat-dose toxicology studies in mice, rats and dogs are summarised below. TK analyses were also conducted for the carcinogenicity and reproductive and developmental toxicity studies (see corresponding sections of the nonclinical AR).

In mice, dose-related increases in Cmax and AUC were less than dose-proportional on Day 1 of the 28-day study, but generally dose-proportional between 5 and 15 mg/kg/day on Day 28. There was considerable oteseconazole accumulation, which increased with increasing dose even though the high dose group were assessed 11 days early. There were no apparent sex-differences in exposure.

In rats, dose-related increases in Cmax and AUC were less than dose-proportional on Day 1 of the 28-day study from 5 to 120 mg/kg/day. On Day 15, exposures increased approximately dose-proportionally from 5 to 25mg/kg/day, but greater than dose-proportionally at higher doses (from 25 to 60mg/kg/day). Dose-proportionality in the 120mg/kg/day group could not be assessed as these animals were sacrificed moribund on day 10. On Day 29 AUC values were approximately 6 to 11-fold higher than Day 1, demonstrating accumulation over the dosing interval. There was no evidence to suggest a gender difference in oteseconazole exposure. Tmax was variable, ranging from 4 to 24 hours. Following the initial rise in concentration over the first 2 hours after dosing on Day 1, plasma concentrations of oteseconazole remained relatively constant over the rest of the 24-hour sampling interval. On Study Days 15 and 29, there were only small changes in oteseconazole concentration over time, often without any discernible peaks in the concentration-time profiles, thereby making it difficult to estimate Tmax. Similar findings are also reported from the TK analyses for the 14-day and 26-week toxicology studies in rats. Of note, in the rat 26-week study an estimate of oteseconazole half-life was reported at week 26, typically exceeding 100 hours. In addition, the accumulation ratio based on AUC in this longer duration study was even higher, ranging from 5.6 to 26.1-fold Day 1 values.

In dogs, on Day 1 of the 28-day study, oteseconazole exposure was variable between animals within each dose-group, but the degree of inter-animal variability tended to be lower on Days 14/15 and 28. Increases in Cmax and AUC were observed across oral doses ranging from 10 to 100 mg/kg/day, but exposures tended to increase in a less than dose proportional manner on all study days. There were no differences in Cmax and AUC between males and females across all dose levels and study intervals. There was accumulation of oteseconazole in plasma during 28 days of dosing, with accumulation ratios ranging from approximately 24 to 65-fold on Day 28. There was also an increase in CL/F with increasing dose in both sexes on Day 28, and within each dose-group males and females showed similar values for CL/F. Tmax on days 1 and 14/15 ranged between 12 and 24 hours, but more variability was reported on day 28, with Tmax values ranging between 0 and 20 hours. Although on Days 14/15 and 28, there were only small changes in oteseconazole concentration over time, often without any discernible peaks in the concentration-time profiles, thereby making it difficult to estimate Tmax. Similar findings are also reported from the TK analyses for the 39-week study in dogs. Of note, half-life values where determined (Day 273 only), were long (exceeding 335 hours). In addition, the

accumulation ratio based on AUC in this longer duration study was even higher, ranging from 95.4 to 126-fold Day 1 values.

3.2.4.7. Other toxicity studies

Phototoxicity

A phototoxicity IC_{50} value of 1.3 μg/mL was reported for oteseconazole in the neutral red uptake phototoxicity assay in BALB/c 3T3 Mouse fibroblasts in the presence of UVR (Study 20056185). However, in line with ICH S10 guidance, the in vitro result is superseded by negative in vivo phototoxicity testing. Hence, in the absence of findings in the GLP-compliant in vivo phototoxicity study in pigmented Long Evans rats (Study 20063967) with dosing up to 240 mg/kg/day once daily for 3 days, the available nonclinical data do not indicate a phototoxicity risk.

3.2.5. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Oteseconazole/ Vivjoa					
CAS-number (if available): 1340593-59-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 123	4.63			Potential PBT (Y)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	4.63			B
Persistence	DT50 or ready biodegradability	Not ready biodegradable, degradation half-life in fresh water is higher than 40 days			P
Toxicity	NOEC or CMR	NOEC (algae) 0.004 mg/L			T
PBT-statement:	The compound is PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, refined (e.g. prevalence data Germany)	0.061	μg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 6204 L/kg (soil) K_{oc} = 30313 L/kg (soil) K_{oc} = 48695 L/kg (soil) K_{oc} = 765 L/kg (sludge) K_{oc} = 1767 L/kg (sludge)			
Ready Biodegradability Test	OECD 301	5% in 28 days			Not readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	3.8	μg/L	*Pseudokirchneriella subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	34.6	μg/L	*Daphnia magna*
Fish Sexual Development Test	OECD 234	NOEC	≥24.0	μg/L	*Danio rerio* (Zebrafish)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	>1000 1000	mg/L	Pre-test

Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	Range: 145.5-165.4	L/kg	lipid normalised steady-state BCF
Sediment dwelling organism	OECD 225	$NOEC_{worm\ number}$ $NOEC_{Biomass}$	125 250	mg/kg	*Lumbriculus variegatus*

3.2.6. Discussion on non-clinical aspects

Pharmacology

Oteseconazole is a novel, orally bioavailable selective inhibitor of fungal lanosterol demethylase (LD, CYP51), with better selectivity for the fungal CYP51 polypeptide than other approved azole antifungals, as demonstrated in *in vitro* primary pharmacodynamics studies. Oteseconazole was shown to have a high binding affinity for *C. albicans* CYP51 (CaCYP51, Kd ≤39 nM). It inhibits CaCYP51 with an IC_{50} of 1.5 µM, an effect equivalent to control azoles, fluconazole, itraconazole and voriconazole (IC_{50}s 1.4 to 1.6 µM) without inhibiting human CYP51 activity at drug concentrations up to 50 µM.

Oteseconazole also showed activity against *Candida*, *Coccidioides* and *Cryptococcus* species as well as dermatophytes and endemic fungi. Oteseconazole was also active against clinical isolates with reduced susceptibility to azoles and echinocandins.

Oteseconazole was shown to directly inhibit a number of human liver CYP enzymes, including CYP enzymes critical for steroid biosynthesis. For CYP19, a key enzyme in the biosynthesis of oestrogens, the IC_{50} for oteseconazole was 7 µM, approximately 180-fold greater than the oteseconazole upper limit Kd value of <=39 nM for fungal CYP51.

The potential for oteseconazole to inhibit steroid biosynthesis was further investigated in a hamster model and oteseconazole did not significantly alter testosterone, progesterone or cortisol levels in male hamsters in a dose range of 10 to 50 mg/kg.

Secondary pharmacodynamic studies assessed potential off-target effects of oteseconazole on non-cytochrome metalloenzymes and a broad panel of receptors, ion channels, and transporters. Oteseconazole was found to significantly inhibit metalloenzymes, endothelin converting enzyme (53%) and 5-lipoxegenase (97%), as well as human adenosine A3 receptor (93%), human melatonin MT1 receptor (81%), rat cerebral cortex Na^+ channel (site 2, 61%), rat cerebral cortex Cl^- channel (GABA-gated, 97%) human norepinephrine transporter (65%) and human dopamine transporter (71%). These findings were not considered clinically relevant due to the high protein binding of oteseconazole.

Although below the significance criteria for the assay (50%), inhibition of thromboxane synthase (36%) was also observed in the metalloenzyme inhibition study, which could be indicative of weak to moderate effects and incidences of haemorrhage were observed in developmental toxicology studies (Section 4.5 of the AR). However, inhibition of thromboxane synthase was not considered of clinical relevance due to high protein binding of oteseconazole and the absence of bleeding or haemorrhage findings in clinical studies.

Safety pharmacology data do not indicate an effect on CNS or respiratory parameters in rats. Oteseconazole did inhibit the hERG potassium current with an estimated IC_{50} of 1.9 µM, but the free oteseconazole at clinically relevant exposures is estimated to be ~50-fold lower than the hERG inhibitory concentration. In addition, no oteseconazole-related changes in heart rate, systolic, diastolic and mean arterial blood pressure, cardiac rhythm or ECG morphology were noted in a cardiovascular safety pharmacology study conducted in telemetered male beagle dogs.

Pharmacokinetics

A comparison of reported PK parameters in dogs between Study 0832DV22.001 and Study 0832DV22.002 at the 10 mg/kg oral dose demonstrates large differences between the two studies, calling into question the reliability of these data due to the level of variability and low numbers of animals included. Sex-related differences in exposure in dogs are reported (Study 0832DV22.002), suggesting lower exposure in males compared to females at 10 and 30 mg/kg. However, as only one dog is included in the study per sex per group, there are insufficient animals at each dose level to draw any conclusion on gender differences from this study. A food effect on the oral bioavailability of oteseconazole in dogs is also reported, based on the data reported in study 028823. The extent of absorption is reportedly different between the fed and fasted dogs following oral administration of 10 mg/kg oteseconazole (2.6 to 3.1-fold greater under the fed condition for Cmax and AUC). However, there is considerable inter-individual variability in the reported exposures in both the fed and fasted state, with some overlap between groups. Furthermore, the magnitude of the difference between the fed and fasted state is less than the difference in exposures reported between study 0832DV00.001 and study 0832DV00.002 (2.6-fold, 6.3-fold, for Cmax and AUC respectively), for which there is no explanation.

Plasma protein binding studies demonstrate that oteseconazole is highly protein bound in all nonclinical species tested and in humans (>96% in mice, >99% in rat, dog and human), with some suggestion of saturation of binding at high concentrations. Tissue distribution was assessed in a quantitative whole body autoradiography study in albino SD rats and partially pigmented Long Evans rats, indicating that oteseconazole is widely distributed, and no specific association with melanin-containing tissues was observed. Oteseconazole exposure was assessed in cross-fostered pups, with results demonstrating that oteseconazole crosses the placenta and is excreted in milk, as exposure in pups was achieved both *in utero* and via milk transfer.

Oteseconazole was not significantly metabolised when incubated *in vitro* with mouse, rat, or human hepatocytes and little to no substrate loss was observed in the presence of various recombinant human CYP enzymes. Only one metabolite, consistent with hydroxylation and glucuronidation of oteseconazole, was detected in dog hepatocytes. Oteseconazole was not a substrate for any of the transporters tested. Oteseconazole was found to be a direct inhibitor of CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A4/5, CYP2C9 and CYP3A4/5 but not CYP1A2. Oteseconazole also induced a number of CYP isoenzymes. However, the applicant assessed the DDI liability of oteseconazole related to *in vitro* CYP inhibition and induction and concluded that there is negligible risk of clinically significant DDIs with oteseconazole and further *in vivo* studies are not required. Oteseconazole inhibited human transporters P-gp, BCRP, OATP1B1, OATPB3, MATE1 and MATE2-K *in vitro*. No significant inhibition of OAT1, OAT3, and OCT2, ASBT, NTCP, or MRP2-mediated transport at up to 10 µM, but oteseconazole did inhibit BSEP-mediated transport. Based on the physicochemical properties (e.g. neutral charge, low aqueous solubility) and the high degree of protein binding of oteseconazole, the risk of clinically relevant transporter inhibition was assessed as low for all of the transporters assessed, with the exception of BCRP.

The primary route of elimination of oteseconazole in rats is via the faeces, which is prolonged, continuing through 504 hours post-dose.

Toxicology

Stand-alone single dose toxicity studies are not required in line with ICH M3(R2) guidance, as acute toxicity information is available from short duration (5-7 days), non-GLP, non-pivotal, oral repeat-dose

toxicity studies in mice, rats and dogs. However, study reports for 2 single dose toxicity studies, one in rats and one in dogs (Study 025745 and Study 0406DV22.001 respectively) were provided. In rats, a single dose NOAEL of >1000mg/kg is reported, although maximal exposure was achieved at the 300mg/kg dose. In dogs, exposure was also maximal in the 300 mg/kg group and an MTD was not defined. A gender-related effect on exposure was reported at higher dose levels, with higher exposure in females at the 100 and 300 mg/kg dose levels compared to males, but only one dog was included in the study per sex per group, which is insufficient to draw any conclusions. Of note, a very long half-life was reported (187 to 512 hours) at all dose levels.

In the pivotal repeat-dose study in CByB6F1 non-transgenic wild-type mice, oteseconazole up to 50 mg/kg/day was administered for 28-days and a NOAEL is reported at the low dose of 5 mg/kg/day. However, at ≥ 5 mg/kg/day hepatocellular effects (including liver vacuolation, increase ALT and AST), adrenal cortical vacuolation, testicular germ cell degeneration, epididymal germ cell debris and loss of corpora lutea are reported. Although these findings were not reported as adverse, the 5 mg/kg/day dose is perhaps more accurately designated as a highest non-severely toxic dose (HNST). A high dose of 5 mg/kg oteseconazole in males and 15 mg/kg/day in females was selected for the 6-month carcinogenicity study.

In a non-GLP acute repeat-dose study in rats, once-daily oral doses of up to 300 mg/kg oteseconazole were administered for 7 days and a NOAEL was not defined due to increased liver weights reported at the lowest dose tested of 30 mg/kg/day, with associated microscopic findings. A second non-GLP acute study in SD rats was conducted to further explore findings reported in male reproductive organs (Study 2130-019). The Applicant reports a NOEL for effects on the male reproductive system at 30 mg/kg/day based on organ weights, histopathology and serum hormone data. However, serum hormone changes were also present in the 30 mg/kg/day dose group (although not considered of relevance to humans due to the absence of effects on circulating hormones in males in clinical trials). These studies are non GLP-compliant, but a validated bioanalytical method was used in Study 2130-019 and while the reported Cmax and AUC in this study are ~ 3.6-fold less than the equivalent Cmax and in study 025949 at the same dose level, it is noted that the vehicle used in these two studies is different, with oteseconazole administered in 20% Cremophor EL in the first study (025949) and 0.5% carboxymethylcellulose (CMC) in the second male study (2130-019).

In a 28-day repeat dose toxicity study in rats, up to 120 mg/kg/day oteseconazole was administered, but the high doses were not tolerated with mortality reported at 60 and 120 mg/kg/day. A NOAEL was not identified due to adverse findings of hepatocellular hypertrophy and necrosis, adrenocortical vacuolation and alveolar histiocytosis at the low dose of 5 mg/kg/day.
A subsequent 14-day study was completed in rats, with dosing up to 5 mg/kg/day. A NOAEL of 3 mg/kg/day was reported due to findings of liver hypertrophy (with coagulative necrosis), adrenocortical vacuolation, and pulmonary alveolar histiocytosis at 5mg/kg/day, which is consistent with the previous 28-day study in rats.
In the pivotal chronic repeat-dose study in rats, dosing up to 5 mg/kg/day was administered for 26-weeks and a NOAEL of 0.5 mg/kg/day is reported, corresponding with a Cmax of 667 ng/mL and AUC_T of 14,500 ng·hr/mL at Week 26. These exposures are considerably lower than the anticipated clinical exposure level under the recommend dosing schedule for oteseconazole for both the VVC and the RVVC indications. However, the liver toxicity was considered a rodent specific effect not relevant for humans, which is supported by the absence of liver findings in the dog studies.

In summary, results from the pivotal repeated dose toxicity studies in rats suggest, no or low safety margins for effects on liver, thyroid, adrenal gland, kidney, lungs, ovaries, and male reproductive system. Nevertheless, changes in liver and thyroid were attributed to hepatic induction of cytochrome

P450 and regarded as adaptive physiologic processes not considered to represent pathologic alterations that would be adverse to humans. Since progressive chronic nephropathy (CPN) is a distinctive entity in rats with no counterpart in humans, oteseconazole-induced exacerbation of CPN in rats was not considered to have any relevance for human risk assessment. Effects observed in adrenal glands, ovaries and lungs were not considered adverse. Findings in the male reproductive system were considered to be secondary to inhibition of CYP17α-hydroxylase activity by oteseconazole, ultimately resulting in decreased testosterone production in the Leydig cells in male rats.

In an acute repeat-dose study in beagle dogs, once-daily oral dosing of up to 300mg/kg/day was well tolerated for 7 days and a NOAEL of 300 mg/kg/day was reported. Results suggested a gender effect on exposure in dogs, with greater exposure achieved in males, which is consistent with the findings reported from the single dose dog study. However, with only one dog per sex per dose in each study and considering the extent of inter-individual variability seen in the single dose PK studies in dogs, there are insufficient animals included at each dose level to draw any conclusion on gender differences from these studies.

In the 28-day repeat-dose study in dogs, up to 100 mg/kg/day oteseconazole was administered by daily oral dosing and a NOAEL of 10 mg/kg/day was reported.
In the pivotal chronic repeat-dose toxicity study in dogs, a loading dose of 0, 0.75, 2.5, 7.5 or 20 mg/kg/day otesecoazole was administered for 5 weeks, followed by maintenance dosing of 0, 0.75, 1.5, 5.5 or 17mg/kg/day oteseconazole, for a total treatment duration of 39 weeks and a NOAEL of 17mg/kg/day is reported, corresponding to a Day 273 mean Cmax of 74,700 ng/mL and $AUC_{0\text{-}24}$ of 1,675,000 ng· hr/mL (≈30- and 22-fold safety margin relative to anticipated human exposure at the MRHD for acute VVC and RVVC, respectively, based upon an AUC comparison). Although findings of increased adrenal weights with moderate to severe hypertrophy/ hyperplasia of the adrenal gland cortex and vacuolation of the zona fasiculata and the significantly decreased prostate gland weights were reported at 17mg/kg/day, but all findings were reversible during the recovery period.

Oteseconazole was negative in a standard battery of GLP-complaint genotoxicity tests.

No test article-related carcinogenicity is reported in the 26-week carcinogenicity study in CByB6F1-Tg(HRAS)2Jic[rash] Transgenic mice. A high dose of 5 mg/kg/day in males and 15mg/kg/day in females was selected for this 6-month carcinogenicity study, on the basis of the findings of the pivotal 28-day repeat-dose toxicity study in mice.

In a long-term carcinogenicity study in SD rats with an intended duration of 104-weeks, once daily oral dosing of up to a 5 mg/kg/day high dose of oteseconazole (reduced to 3 mg/kg/day during the study) was administered for a maximum of 91 weeks, due to a high incidence of mortality in all oteseconazole-treated groups. Neoplastic oteseconazole-related effects are reported in the thyroid gland, liver, testes, and uterus as follows: benign follicular cell adenoma in the thyroid gland of both sexes at ≥ 1.5 mg/kg/day; malignant follicular cell carcinoma in the thyroid gland in males at ≥ 1.5 mg/kg/day and in females at 5/3 mg/kg/day; benign hepatocellular adenomas in males at ≥ 0.5 mg/kg/day; malignant hepatocellular carcinomas in females at 5/3 mg/kg/day; benign Leydig cell adenoma in the testes at ≥ 1.5 mg/kg/day; benign granular cell tumour in the uterus at 5/3 mg/kg/day. No unscheduled deaths directly attributed to oteseconazole-related neoplastic findings are reported. This tumour development in rats following chronic treatment with oteseconazole, is considered secondary to species-specific mechanisms of hepatic microsomal enzyme induction (thyroid and liver tumours) and increased concentrations and luteinizing hormone (Leydig cell tumours). . The proposed mechanism of species-specific induction of thyroid, liver, and testicular tumours in rats is

plausible and supported by the absence of tumorigenic findings in the Tg mouse study. However, the possible clinical relevance of oteseconazole-induced benign granular cell tumour in the uterus in rats cannot be excluded and these findings are included in section 5.3 of the SmPC.

DART studies characterising adverse effects of oteseconazole on mammalian reproduction were conducted in line with ICH S5(R3), including the following GLP compliant pivotal studies; fertility and early embryonic development (FEED) studies in males and females, embryo foetal development (EFD) studies in two species, rats and rabbits; and a pre- and post-natal development (PPND) study in rats. Four additional PPND studies were also conducted in SD and HAN Wistar rats, with the aim of further characterising the ocular toxicity findings in the F_1 generation from oteseconazole-treated dams identified in pivotal PPND study in SD rats. However, considering a hazard related to the findings of ocular toxicity was already identified in the pivotal study, and data from the additional PPND studies do not to de-risk these findings, the rationale for conduction the additional 4 PPND studies is questionable and not in line with 3Rs principles for the use of experimental animals.

In the male FEED study, test-article related effects on sperm parameters (motility and morphology) but not on fertility are reported and a NOAEL of 3mg/kg/day for sperm parameters, and 10mg/kg/day for general toxicity is reported. In the female FEED study, test-article related decreased fertility and fecundity indices (76% vs 96% in controls), increased post-implantation losses (9.37% versus 3.71% in controls) and increased mean number of resorptions (1.3 vs 0.5) are reported at 25mg/kg/day, which were statistically significant from controls but within the range of historical control data. A NOAEL for reproductive and fertility parameters in females was reported as 5 mg/kg/day, although the NOAEL for general toxicity in females was reported as 1.5 mg/kg/day, due to findings of decreased body weight gain. The effects observed on female fertility should be considered potentially relevant to the intended patients' population of the medicinal product, particularly in light of the relative low safety margin (2.7-fold).

In the rat EFD study, oteseconazole-related maternal toxicity is reported at 40mg/kg/day, with lower gestational body weight, reduced body weight gain and reduced food consumption during the treatment period. Based on these data, a NOAEL for maternal toxicity of 10mg/kg/day is reported. However, there was no evidence of teratogenicity of the test article reported and a NOAEL at the high dose of 40mg/kg/day is reported for developmental toxicity. In the rabbit EFD study, maternal toxicity was evident at the high dose of 15mg/kg/day and mean foetal body weights were also significantly lower, although no teratogenic effects were noted. A NOAEL for maternal and developmental toxicity was reported at 5mg/kg/day. The findings from the EFD studies in rabbits are included in section 5.3 of the SmPC.

In the pivotal PPND study in rats, a NOAEL for maternal toxicity and effects on gestation, parturition and lactation was identified at the high dose of 7.5 mg/kg/day. However, in the offspring, test-article related lower mean body weight gain and ocular toxicity was reported in F_1 pups of 7.5 mg/kg/day treated dams and a NOAEL of 3 mg/kg/day was reported for F_1 growth and eye development. Additionally, some F_1 mortality is reported, but this was not considered treatment related in the absence of a clear dose-response.

An investigational PPND study in SD rats was carried out, with ophthalmology evaluations beginning after eye opening until at least PND50. Consistent with the previous pivotal study, no test article-related effects on dams were reported but treatment-related toxicity was reported in F_1 pups, including decreased body weight gain and ocular toxicity. Of note, significant post-weaning mortality occurred in F_1 generation pups (n=84 deaths), attributed to excessive haemorrhage following sub-cutaneous microchip implantation on PND21.Consistent with this, in a second investigational PPND study in SD rats, there were no test article-related effects on dams and test-article related mortality in the F_1

generation was also reported, although the incidence of mortality was markedly lower. Ocular toxicity and altered coagulation parameters are also reported in this study.

A third investigational PPND study was conducted in SD and Han Wistar rats. No test article-related effects were reported on dams consistent with previous studies, with the exception of increased mean body weight gains, noted in both strains during lactation. This treatment-related effect, resulting in higher mean body weights in these groups vs their respective control groups, was not considered adverse. Paradoxically, mean food consumption in the 7.5 mg/kg/day SD group was lower compared to the SD control group during the lactation dosing period. Treatment-related mortality in F_1 generation was reported pre-weaning (n=2 SD pups) and post-weaning (n=1 SD + n=1 HAN). Test-article related findings of tremors and swollen abdomen were common to F_1 pups of both strains, and findings of swollen abdomen continued throughout the post-weaning period. Additionally, adverse treatment-related findings of sub-cutaneous haemorrhage, pale eyes, lower mean body weight and body weight gain, were reported in the offspring of oteseconazole-treated SD rats. Mortality in the HAN offspring was associated with soft eyes and opacity in both eyes. Ocular toxicity, including enophthalmus and dark red discoloration were noted in F_1 SD rats, with exophthalmus reported in the F_1 HAN group. While these eye findings were observed at low incidence in these groups, they were considered test article-related based on similarity to findings observed for previous studies. Treatment-related cataracts were also observed in F_1 pups from both rat strains. Alterations in hematology, coagulation, and serum chemistry parameters were also noted in F_1 generation animals, with higher severity in the SD rats.

These data suggest that maternal oteseconazole treatment-related ocular toxicity in F_1 pups is not stock or strain specific, as it has been demonstrated to occur in two different stocks of SD rats [Crl:CD(SD) and Hsd:SD] and in a different strain of rats (Han Wistar). Oteseconazole-related coagulopathy also appears to be a common issue across stocks and strains, with subcutaneous haemorrhage reported in Hsd:SD rats in this study, and effects on clinical pathology parameters (hematology, coagulation, and serum chemistry) reported in both SD and Han Wistar rats in this study. Although the human relevance of these findings is unknown, these additional PPND studies do not de-risk the findings of developmental toxicity (ocular toxicity and coagulopathy) associated with maternal oteseconazole treatment identified in the pivotal study.

In the cross-fostering PPND study in SD rats, no treatment-related adverse effects on dams were reported. In F_1 pups, an oteseconazole-related, non-adverse increase in visceral variation innominate artery- absent was noted, but no effect of oteseconazole exposure or cross-fostering was noted on F_1 survival, clinical observations, body weight, ophthalmic observations, or macroscopic observations. Hence, in contrast to findings from the previous study in Hsd:SD rats, a no observed adverse effect level is reported at 7.5 mg/kg/day for this study. However, as this study failed to replicate the findings from Study 01234004 at the same dose level, using the same stock and strain of rats, the absence of toxicity reported in the cross-fostering groups is not informative, and the inconsistency across studies is unexplained. Therefore, inclusion of data from this study in section 5.3 of the SmPC was not agreed, as the absence of toxicity in the cross-fostering groups was not considered meaningful or of relevance to the prescriber (see attached annotated SmPC for further details).

In response, the Applicant conducted a second cross-fostering study (Study No. 9002150) with administration of oteseconazole at 7.5 mg/kg/day. This study employed two different drug substance batches and both Hsd and Crl Sprague Dawley rats. As for the first cross-fostering study, the new study revealed no oteseconazole-related ocular findings in the F1 generation.

As a possible explanation for the absence of toxicity in the first cross-fostering study, the Applicant referred to the incidence rate of spontaneous ocular lesions, which, according to the response, generally

exceeds that associated with oteseconazole exposure in F1 pups at 7.5 mg/kg/day. According to the information provided, several groups have reported incidence rates of spontaneous ocular findings in 3- to 7-week old (PND 21-PND 49) Sprague Dawley rats assessed by detailed ophthalmologic examination as part of pre-test general toxicology screens. The incidence rate of spontaneous ocular lesions in the lens of these rat pups (cataract: 1-40%) generally exceeded that associated with oteseconazole exposure in F1 pups at 7.5 mg/kg/day. These external historical data are considered useful in characterizing ocular abnormalities in developing Sprague Dawley pups and serves as a quality control tool for establishing the reasonableness of the spontaneous eye findings in rat pups of similar age and strain.

The lack of compound-related ocular toxicity in the two consecutive cross-fostering studies was considered to suggest that the variable natural background incidence may interfere with unequivocal judgement of the safety risk for humans associated with these nonclinical findings of ocular toxicity in rat pups. The Applicant considered that it is of relevance to also include data from the cross-fostering PPND studies in Section 5.3 of the SmPC. However, other than a possible issue related to spontaneous incidence, which could lead to the conclusion that the ocular findings are not to be attributed to oteseconazole, there seems to be no other apparent explanation for the lack of ocular effects in the two cross-fostering studies.

Overall, the two cross-fostering studies are inconclusive as to whether the ocular effects observed in the previous PPND studies are due to exposure oteseconazole during gestation and/or lactation. Before a conclusion is reached on whether the ocular effects observed in these previous PPND studies are to be attributed to oteseconazole and the information to be included in the SmPC, a further discussion on the findings is needed. The Applicant should provide a further discussion on the ocular observations at 7.5 mg/kg/day in the different studies (including the two cross-fostering studies), which also takes into account, among others, how the incidences compare to those in the historical control for the rats used in the studies, and how the presence and incidence of ocular findings in the different studies may be related to maternal systemic exposures to oteseconazole, the ocular-related endpoints used in the different studies and pup general toxicity (e.g. effects in body weight gain) and number of animals per group **(OC)**.

Exposure margins are calculated based on TK data from the pivotal repeat-dose toxicology studies in mice, rats and dogs and the following oteseconazole exposures in humans:

For acute VVC exposure is estimated based upon an oteseconazole dosing regimen of 600 mg on Day 1, 450 mg on Day 2 [End of Day 2: Cmax = 2,000 ng/mL; AUC0-24 = 48,000 ng·hr/mL (Cmax x 24); VMT-VT-1161-CL-017, a Phase 3 study in subjects with RVVC].

Oteseconazole exposure in humans for RVVC is estimated based upon the following oteseconazole dosing regimen: 600 mg on Day 1, 450 mg on Day 2, then 150 mg weekly for up to 11 weeks starting at Week 2 [End of Week 12: Cmin = 2,700 ng/mL; AUC0-24 = 64,800 ng·hr/mL (Cmin x 24); VMT-VT-1161-CL-017, a Phase 3 study in subjects with RVVC].

Environmental risk assessment

The applicant commits to provide a report on the transformation in water sediment systems according to the OECD 308 study by the end of 2026. Once the OECD 308 study has been completed and an updated overall ERA report should also be submitted.

In addition, the applicant was asked to repeat the study on aquatic bioaccumulation (OECD 305) using radiolabelled test substance because the validation criteria failed and the TOC exceeded the maximum value. The applicant provided a justification for why deviations from the ± 20% recovery rates occurred, attributing this to difficulties preparing the stock solutions, but since the numbers of the

concentration analysis performed for determination of the steady-state concentrations of the test item in the fish were more than required by the guideline (and covered approximately a 5-days period) the applicant considered the obtained steady-state concentrations and the calculated BCFs reliable. However, uncertainties regarding the assessment of bioaccumulation behaviour remain as the test substance concentration could not be kept constant in water as required for compliance with the validity criterion. Furthermore, the TOC concentration exceeded the specified value of ≤ 2 mg/l in the dilution water before test start. As a consequence, a loss of test substance due to adsorption to particles and glass surfaces is enhanced. Also, there are deviations in body weight, abnormal high lipid contents, missing statistics and insufficient kinetic evaluation. Moreover, information about the potential formation of metabolites cannot be deduced, since the applicant did not use a labelled test substance.

These uncertainties require a worst-case estimation with the available data to ensure that the BCF is in a range below 2000. Therefore, the applicant is asked to calculate the individual BCFs of each sampling and include these results to the to study report and ERA. If the maximum value exceeds 2000 the active substance is classified as PBT. Furthermore, the applicant should add an explanation why the TOC in the dilution water exceeds the 2 mg/l trigger (**OC**).

As a result of the above consideration, the available data do not allow to conclude definitively on the potential risk of oteseconazole to the environment, including the PBT classification. If the substance is identified as a PBT substance, this will need to be included in sections 5.3 and 6.6 of the SmPC.

3.2.7. Conclusion on non-clinical aspects

There are no major objections raised on the nonclinical package submitted in support of oteseconazole. There are a number of outstanding other concerns regarding the non-clinical data, ERA and the proposed non-clinical wording in SmPC, which must be addressed prior to approval of this MAA. The applicant will resolve one of the outstanding issues regarding the environmental risk assessment by a post-approval commitment to provide the additional required study data (OECD 308) within 3 years.

3.3. Clinical aspects

- **Tabular overview of clinical studies**

The Phase 1 studies during which PK data were obtained are listed in the table below.

Two additional Phase 1 studies not in the table are:

- **CL-020**, which assessed the effect of renal impairment on oteseconazole PK; and
- **RGL-004-002**, which compared the bioavailability of oteseconazole after dosing with a 150 mg hard capsule manufactured by two different facilities.

During the procedure, the applicant completed and reported the CSR for a Phase 1 study (**CL-019**) in female subjects with hepatic impairment.

Type of Study	Study Identifier	Location of Study	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen;	Number of Subjects	Healthy Subjects or	Duration of	Study Status
Phase 1 Studies									
First-in-human, single dose escalation	VMT-VT-1161-CL-001	5.3.3.1	Safety, Tolerability, PK	Single-center, randomized, double-blind, placebo-controlled	OTE; 5, 10, 20, 40, 80, 160, or 320 mg QD; Oral	64/64/60	Healthy Subjects	1 day	Completed
Multiple dose-escalation	VMT-VT-1161-CL-002	5.3.3.1	Safety, Tolerability, PK	Single-center, randomized, double-blind, placebo-controlled	OTE; 40, 80, 160, and 320 mg QD; Oral	32/32/31	Healthy Subjects	7 days	Completed
CYP3A4 DDI and PKE	VMT-VT-1161-CL-007	5.3.3.4	Safety, Tolerability, PK	Single-center, open-label	DDI Cohort OTE; 600 mg QD; Oral[a]	28/28/24	Healthy Subjects	14 days	Completed
					PKE Cohort OTE; 600 mg QD; Oral	8/8/8	Healthy Subjects	1 day	
Ethno-bridging	VMT-VT-1161-CL-008	5.3.3.3	Safety, Tolerability, PK	Single-center, open-label	OTE; 300 mg or 600 mg QD; Oral	51/51/45	Healthy Subjects (Japanese and Western)	14 days	Completed
Food effect	VMT-VT-1161-CL-013	5.3.1.1	PK	Single-center, open-label	OTE; 150 mg QD; Oral	44/44/44	Healthy Subjects	1 day	Completed
Oral contraceptives DDI	VMT-VT-1161-CL-014	5.3.3.4	Safety, Tolerability, PK	Single-center, open-label	OTE; 150 mg QD; Oral[b]	24/24/24	Healthy Subjects	14 days	Completed
P-gp and BCRP DDI	VMT-VT-1161-CL-015	5.3.3.4	Safety, Tolerability, PK	Single-center, open-label	P-gp Cohort OTE; 150 mg QD; Oral[c]	24/24/23	Healthy Subjects	14 days	Completed
					BCRP Cohort OTE; 150 mg QD; Oral[d]	24/24/24	Healthy Subjects	14 days	
ADME	VMT-VT-1161-CL-016	5.3.3.1	PK	Single-center, open-label, mass balance	OTE; 600 mg/5 µCi [^{14}C]-VT-1161 QD; Oral	10/10/9	Healthy Subjects	1 day	Completed
QT Study	VMT-VT-1161-CL-018	5.3.3.2	Safety, Tolerability	Single-center, double-blind, PK study	OTE 600 mg/1200 mg (QD) Oral	60/59/56	Healthy Subjects	14 days	Completed

There were 4 Phase 2 trials and three Phase 3 trials.

For the prevention of recurrent vulvovaginal candidiasis (RVVC)

There was one Phase 2 dose-finding study (**CL-006**) and three Phase 3 studies **(CL-011, -012** and -**017**). Due to overlapping study design, the methods section describes the three Phase 3 studies together, pointing out specific differences. Only CL-017 used the exact final recommended posology so the results of this study are described first, followed by those of CL-011 and -012.

For the treatment of acute VVC

The data from **CL-017** are pivotal.

The Phase 2 study **CL-004** was conducted in women with acute VVC but it did not use the final posology and it is not described in this Overview.

Phase 2 Studies									
Proof-of-concept	VMT-VT-1161-CL-003	5.3.5.4	Efficacy, Safety, Tolerability, PK	Multi-center, randomized, double-blind, parallel-group placebo-controlled	OTE; 200/50, 600/150, or 600/300 mg QD;[e] Oral	50/50/43	Tinea Pedis	14 days	Completed; Granular
Proof-of-concept	VMT-VT-1161-CL-004	5.3.5.1	Efficacy, Safety, Tolerability, PK	Multi-center, randomized, double-blind, parallel-group active-controlled	OTE; 300 or 600 mg QD, or 600 mg BID FLU; 150 mg QD;[f] Oral	55/55/48	Acute VVC	3 days	Completed; Granular
Dose range-finding	VMT-VT-1161-CL-005	5.3.5.4	Efficacy, Safety, Tolerability, PK	Multi-center, randomized, double-blind, placebo-controlled, parallel-group	OTE; 300 or 600 mg QD for 2 w followed by 300 or 600 mg QW for 10 or 22 w; Oral	259/259/222	OM	84 or 168 days	Completed; Granular
Dose range-finding	VMT-VT-1161-CL-006	5.3.5.1	Efficacy, Safety, Tolerability, PK	Multi-center, randomized, double-blind, placebo-controlled, parallel-group	OTE; 150 or 300 mg QD for 1 w followed by 150 or 300 mg QW for 11 or 23 w; Oral[g]	215/211/176	RVVC	84 or 168 days	Completed; Granular
Phase 3 Studies									
Pivotal	VMT-VT-1161-CL-011	5.3.5.1	Efficacy, Safety	Multi-center, randomized, double-blind, placebo-controlled, parallel-group	OTE; 150 mg QD for 1 w followed by 150 mg QW for 11 w; Oral[g]	326/326/273	RVVC	84 days	Completed; Granular
Pivotal	VMT-VT-1161-CL-012	5.3.5.1	Efficacy, Safety	Multi-center, randomized, double-blind, placebo-controlled, parallel-group	OTE; 150 mg QD for 1 w followed by 150 mg QW for 11 w; Oral[g]	330/327/282	RVVC	84 days	Completed; Granular
Critical	VMT-VT-1161-CL-017	5.3.5.1	Efficacy, Safety	Multi-center, randomized, double-blind, positive-controlled (placebo and FLU), parallel-group	OTE; 600 mg Day 1, 450 mg Day 2 then starting on Day 14, 150 mg QW for 11 w FLU; 150 mg QD for 3 sequential doses;[i] Oral	219/218/167	RVVC	84 days	Completed; Granular

Two other Phase 2 trials were not conducted in VVC (**CL-003** in tinea pedis and **CL-005** in onychomycosis) and are not described in this Overview.

3.3.1. Clinical pharmacology

3.3.1.1. Pharmacokinetics

Bioavailability

CL-001 was a single dose study in healthy adults who received one of 5, 10, 20, 40, 80, 160 mg or 320 mg in the fasting state or 320 mg in the fed state (high fat and kcal meal).

Oteseconazole was absorbed relatively slowly with median Tmax from 4-10 h. Cmax increased slightly less than proportionally to the increase in dose. AUC_{inf} values generally increased with increase in dose. Inter-subject variability was moderate with coefficients of variation ranging from 15 to 43%. Estimates of $t_{1/2}$ were hampered by limited data points but median half-lives were 393-1467 h.

CL-002 was a multiple dose study in healthy adults who received 40, 80, 160 or 320 mg or matching placebo administered once daily for 7 days after a high fat meal.

Oteseconazole was slowly absorbed (median Tmax 6-7 h). The accumulation ratios based on comparing Day 1 and 7 AUC_T values were in the range 4.46 to 6.16 and greatest at the highest dose levels. There was relatively low inter-subject variability during 24 h after dosing on Days 1 and 7 (e.g. 13-25% for Cmax and AUC). The mean Cmax increased in proportion to dose for 40, 80 and 160 mg groups but increased only 1.4-fold between 160 mg and 320 mg. The median half-life after the last dose ranged from 1905 h (79 days) to 3046 h (127 days). As in CL-001, the accuracy of the half-life estimations is limited by duration of sampling.

Table 11-2. Mean (CV%) Noncompartmental Pharmacokinetic Parameters for VT-1161 by Cohort – Day 1

Treatment	C_{max} (ng/mL)	T_{lag}* (h)	T_{max}* (h)	$AUC_{(0\text{-}24)}$ (h*ng/mL)
40 mg	177 (25.5)	1.50 (1.00-2.00)	6.00 (4.00-6.00)	2148 (21.7)
80 mg	341 (17.0)	1.50 (1.50-2.00)	7.00 (6.00-12.00)	4764 (25.0)
160 mg	650 (15.4)	1.00 (0.50-2.00)	6.00 (4.00-8.00)	8428 (13.5)
320 mg	929 (23.7)	1.25 (1.00-3.00)	6.00 (4.00-12.00)	11357 (17.3)

*Median and range

Table 11-3 Mean (CV%) Noncompartmental Pharmacokinetic Parameters for VT-1161 by Cohort – Day 7

Treatment	Cmax (ng/mL)	Tmax* (h)	Cmin (ng/mL)	AUC_T (h*ng/mL)	Cavg (ng/mL)	Racc	Fluctuation (%)	$t_{½}$ (h)
40 mg	531 (19.9)	4.00 (4.00-4.00)	315 (22.7)	10202 (22.4)	425 (22.4)	4.76 (6.6)	51.7 (16.1)	1905 (869-3759)
80 mg	1130 (33.6)	6.00 (6.00-8.00)	742 (42.5)	23143 (38.3)	964 (38.3)	4.46 (17.4)	42.1 (26.7)	2043 (1231-4904)
160 mg	1920 (23.2)	5.00 (4.00-6.00)	1250 (25.6)	38661 (25.3)	1610 (25.3)	4.62 (25.4)	42.1 (18.6)	2921 (1467-6198)
320 mg	3300 (26.1)	4.00 (4.00-8.00)	2240 (31.4)	67164 (22.9)	2800 (26.9)	6.16 (39.9)	38.6 (15.9)	3046 (2262-10746)

*Median and range.

Bioequivalence

CL-013 compared the bioavailability of 150 mg capsules used in Phase 3 and 150 mg tablets used in Phase 2 in 44 healthy adult female subjects. The capsules were given after a high fat, high calorie meal (cohort 2) and after a low fat, low calorie, meal (cohort 3), as well as in the fasting state (cohort 1). Cohort 4 received the 150 mg tablet after a high-fat, high-calorie meal. Tmax was 6 h for the capsule and tablet. Mean Cmax was similar, but AUC_{0-72} was about 13% higher for the capsule vs. tablet.

Table 11–5 Summary of Plasma VT-1161 Pharmacokinetic Parameters Following the Administration of a Single 150 mg VT-1161 Capsule or Tablet Under Fed Conditions: Cohorts 2 and 4 (PK Population)

Pharmacokinetic Parameters	Cohort 2	Cohort 4
AUC_{0-72} (ng*hr/mL)	23200 (30.4) [n=12]	20600 (17.1) [n=8]
C_{max} (ng/mL)	781.2 (34.9) [n=12]	793.7 (18.6) [n=8]
T_{max} (hr)	6.000 (3.99, 24.01) [n=12]	6.001 (2.00, 8.00) [n=8]
Cohort 2: A single 150 mg VT-1161 capsule, high-fat, high-calorie meal (Reference) Cohort 4: A single 150 mg VT-1161 tablet, high-fat, high-calorie meal (Test) AUC_{0-72} and C_{max} values are presented as geometric mean and geometric CV%.		

RGL-004-002 compared the bioavailability of oteseconazole after administration of a single dose of 150 mg using hard capsules manufactured by facility 1 (reference; measured content 100.8%) or facility 2 (test; measured content 99.7%). The latter is the manufacturing site proposed to supply the EU market. Dosing was 30 min after completion of a high fat and high kcal breakfast and samples were obtained for 72 h post-dose. With an estimated 43% inter-subject variability and a difference between the treatment means of 10% or less, the sample size for an 80% probability of the 90% CI of the treatment means ratio to be within the 80.00 to 125.00% range was estimated to be 304 subjects and 340 subjects were enrolled.

There was slightly lower bioavailability for oteseconazole from the facility 1 vs. facility 2 capsules. The 90% CIs for the GMRs were between 80.00 and 125.00% but the upper bounds were below 1.0.
A significant treatment effect was detected by ANOVA for oteseconazole AUC_{72} (p=0.0003) and Cmax (p<0.0001) parameters.

Table 2.7.1-23. Bioequivalence evaluation of oteseconazole in RGL-004-002

Pharmacokinetic parameter	Contrast	Geometric Mean Ratio Test/Ref	90% Confidence Intervals	CV%[1]
C_{max} (ng/mL)	A vs B	90.01	86.25 - 93.94	24
AUC_{72} (hr*ng/mL)	A vs B	90.40	86.37 - 94.62	26
AUC_{inf} (hr*ng/mL)	A vs B	-	-	-

[1] Estimated from the Residual Mean Squares.

Influence of food

CL-001 explored the effect of a high-fat meal with 320 mg single doses given after an overnight fast of at least 10 h or 30 min after a high fat and high kcal meal (900 kcal and 50% from fat). Administration with food gave a 3-fold increase in Cmax and AUC_{inf} increased approximately 4-fold.

CL-013 was the definitive food effect study. The mean Cmax and AUC_{0-72} were higher with dosing after a high fat and high kcal meal (cohort 2) compared to fasting (cohort 1). There were much smaller differences when dosing was after a low fat and low kcal meal (cohort 3) compared to fasting.

Table 11–2 Summary of Plasma VT-1161 Pharmacokinetic Parameters Following the Administration of a Single 150 mg VT-1161 Capsule Under Fasted and Fed Conditions: Cohorts 1 Through 3 (PK Population)

Pharmacokinetic Parameters	Cohort 1	Cohort 2	Cohort 3
AUC_{0-72} (ng*hr/mL)	17110 (24.5) [n=12]	23200 (30.4) [n=12]	17430 (14.6) [n=11]
C_{max} (ng/mL)	538.0 (32.6) [n=12]	781.2 (34.9) [n=12]	629.3 (16.3) [n=11]
T_{max} (hr)	5.019 (4.00, 6.04) [n=12]	6.000 (3.99, 24.01) [n=12]	4.023 (4.00, 6.11) [n=11]
Cohort 1: A single 150 mg VT-1161 capsule, fasted (Reference) Cohort 2: A single 150 mg VT-1161 capsule, high-fat, high-calorie meal (Test) Cohort 3: A single 150 mg VT-1161 capsule, low-fat, low-calorie meal (Test)			

Based on the GMRs, Cmax and AUC_{0-72} were approximately 45% and 36% higher, respectively, when dosing after a high-fat, high-calorie meal vs. the fasted state. There was no major difference between dosing with a low-fat, low-calorie meal and under fasted conditions.

Table 11–3 Summary of Statistical Comparisons of Plasma VT-1161 Pharmacokinetic Parameters Following the Administration of a Single 150 mg VT-1161 Capsule Under Fasted and Fed Conditions: Cohort 2 (High-Fat, High-Calorie Fed) Versus Cohort 1 (Fasted) (PK Population)

	Cohort 2 (Test)		Cohort 1 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Inter-subject CV%
AUC_{0-72} (ng*hr/mL)	23200	12	17110	12	135.64	114.98 - 160.00	24.23
C_{max} (ng/mL)	781.2	12	538.0	12	145.20	119.05 - 177.09	29.31
Cohort 1: A single 150 mg VT-1161 capsule, fasted (Reference) Cohort 2: A single 150 mg VT-1161 capsule, high-fat, high-calorie meal (Test)							

Table 11–4 Summary of Statistical Comparisons of Plasma VT-1161 Pharmacokinetic Parameters Following the Administration of a Single 150 mg VT-1161 Capsule Under Fasted and Fed Conditions: Cohort 3 (Low-Fat, Low-Calorie, Fed) Versus Cohort 1 (Fasted) (PK Population)

	Cohort 3 (Test)		Cohort 1 (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Inter-subject CV%
AUC_{0-72} (ng*hr/mL)	17430	11	17110	12	101.88	86.04 - 120.63	24.23
C_{max} (ng/mL)	629.3	11	538.0	12	116.98	95.48 - 143.31	29.31
Cohort 1: A single 150 mg VT-1161 capsule, fasted (Reference) Cohort 3: A single 150 mg VT-1161 capsule, low-fat, low-calorie meal (Test)							

Distribution

In the mass balance study **CL-016**, the plasma and whole blood radioactivity levels were similar, with the highest values in samples obtained at 4-10 h post-dose. The mean ratio of whole blood to plasma total radioactivity was approximately 1, indicating uptake of radiolabelled drug-related material into blood cells. The $t_{1/2}$ of $^{[14C]}$oteseconazole drug-related materials in human plasma and whole blood was similar to that for unlabelled parent drug.

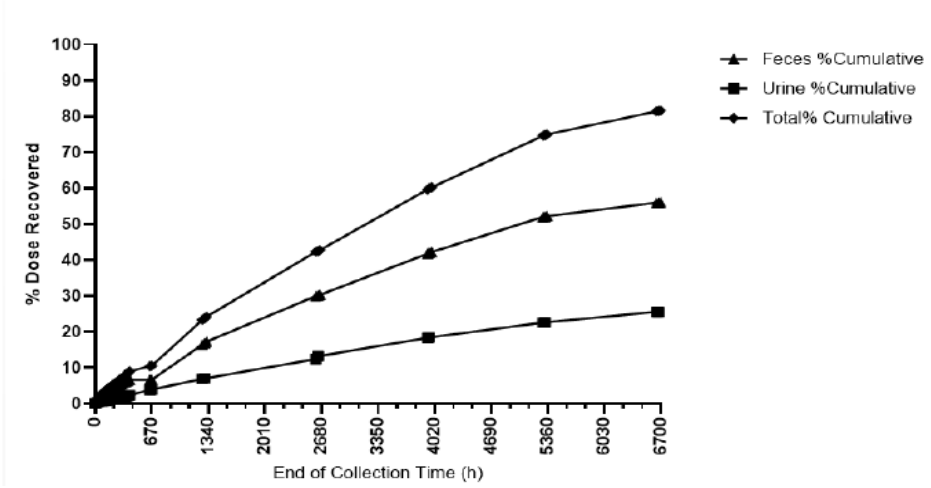
The in-vitro plasma protein binding of oteseconazole was compared across species using mouse, rat, dog and human plasma spiked with 260, 2500, 26000 and 105000 ng/mL of oteseconazole using equilibrium dialysis and 18 h incubation at 37°C. Plasma protein binding of oteseconazole was very high, with a slight suggestion of saturation of binding at the highest concentration tested. However, in a second study using 5 µM oteseconazole (2635 µg/L), plasma protein binding was estimated at 99.8% compared with 10.9% for fluconazole.

Excretion

CL-016 was conducted in healthy adult female subjects (8 completed) aged 18 to 65 years with a mean age of 54.4 years. On Day 1, each received a single oral dose of 600 mg oteseconazole / 5 µCi [14C] oteseconazole immediately after a high fat and high kcal meal. Samples were collected over 17 days post-dose with intermittent sampling up to Day 279 (~10 months), at which time the radiolabel concentrations in plasma and whole blood were >LLOQ for all subjects remaining in the study.

The mean cumulative recovery over the initial collection period (0-408 h) was 8.92%, with 6.32% in faeces and 2.29% in urine. Cumulative recovery increased with time and by Day 278 81.6% of the radiolabel was recovered in the urine and faeces. Based on mean recovery of label, faeces was the primary route of excretion accounting for 56.0% with urine accounting for 25.6%. The unchanged test compound represented approximately 38% of faeces radioactivity, which is equivalent to 21.5% of excreted total drug-related material. It was concluded that the majority of the unchanged test compound observed in the pooled faeces sample (0-408 h) was the product of hepatic excretion.

Figure 2 VMT-VT-1161-CL-016: Mean Cumulative Percent Recovery in Feces, Urine, and Total following a Single, Oral Dose of 5 µCi/600 mg [^{14}C]-VT-1161



Metabolism

In CL-016, metabolite identification in plasma samples was not performed because unchanged parent drug represented 97.06% of the radioactivity recovered in the 0–408 h plasma extract (based on HPLC-UV retention times). Pooled samples of urine and homogenised faeces collected up to 408 h were subjected to metabolite profiling. Based on LC-UV retention times, unchanged oteseconazole was not observed in the 0-408 h urine pool and was provisionally identified as the major radioactive component in the pooled faeces extract, accounting for 38.33% of the total radioactivity (21.46% of excreted drug related material). Additionally, one main metabolite was observed in the 0-408 h urine pool and two in the faeces pool.

Each peak from the metabolite profiles of oteseconazole in human urine and faeces that represented more than 5% of excreted TDRM was selected for identification. Altogether these four peaks represented approximately 64% of excreted TDRM, which is about 78% of the recovered quantity of radioactivity (81.7%).

Matrix	Peak No.	Retention time [min]	% Region of interest	Cumulative Recovery %*	% of excreted total drug-related material (TDRM)
Urine	U1	12.5	62.75	25.6	16.06
Faeces	F1	15.5	21.06	56.1	11.81
	F3	17.25	25.27		14.18
	F5**	24.75	38.33		21.50
Altogether				81.7	63.55

* Cumulative Recovery % for total radioactivity in human urine and faeces are taken from the human mass balance study No. 176-001
**F5 was found to be identical to the unchanged test compound oteseconazole based on its retention time

Final POPPK report

The report covers 10418 plasma concentrations from 158 healthy subjects and 1007 subjects with fungal infections, including PK data from the Phase 3 studies (CL-011, 012 and 017). In Phase 3 studies, plasma levels were determined on Day 14 (before starting weekly dosing), at end of treatment and 36 weeks later. Mean plasma levels on Day 14 and Week 12/14 are shown below.

Table 2.7.2-29. Oteseconazole Plasma Concentrations – Comparison across Phase III Studies

Study	Oteseconazole Dosing Regimen	Day 14 Plasma Concentration (µg/L) (Mean (SD))	Maintenance Phase Week 12* Plasma Concentration (µg/L) (Mean (SD))
CL-011	150 mg QD for 7 days followed by 150 mg QW for 11 weeks	1676.2 (876.27)	3402.4 (1970.51)
CL-012	150 mg QD for 7 days followed by 150 mg QW for 11 weeks	1785.5 (747.75)	3605.8 (1518.08)
CL-017	600 mg on Day 1and 450 mg on Day 2 followed by 150 mg QW for 11 weeks	1396.9 (709.00)	2679.3 (1318.94)

Abbreviations: SD=standard deviation; QD=once daily; QW=once weekly
* Week 12 in CL-011/CL-012 and Week 14 in CL-017 are both post 11 weeks of 150 mg QW dosing, i.e., at the end of Maintenance Phase in all 3 studies.

The initial structural base model was a two-compartment linear model with first-order absorption, an absorption lag time and first-order elimination, based on the previous model structure. The Phase 3 data appeared insufficient to identify enterohepatic circulation (EHC) and it was not further evaluated.

The pre-specified covariate hypotheses were:

- The effects of body weight on clearance and volume parameters, using an allometric exponent. The exponents were to be estimated if feasible; otherwise, the exponents were fixed to 0.75 for clearance and 1.0 for volume
- The effect of CL-002 on apparent central volume of distribution using an exponential model (found in the initial POPPK analysis)
- The effect of formulation (i.e. with and without over encapsulation) on bioavailability
- The effect of CL-007 on Ka using an exponential model (from the initial POPPK analysis)
- The effect of serum bilirubin on apparent clearance using a power model
- The effect of race on apparent clearance using an exponential model
- The effect of serum albumin on apparent central volume of distribution using a power model

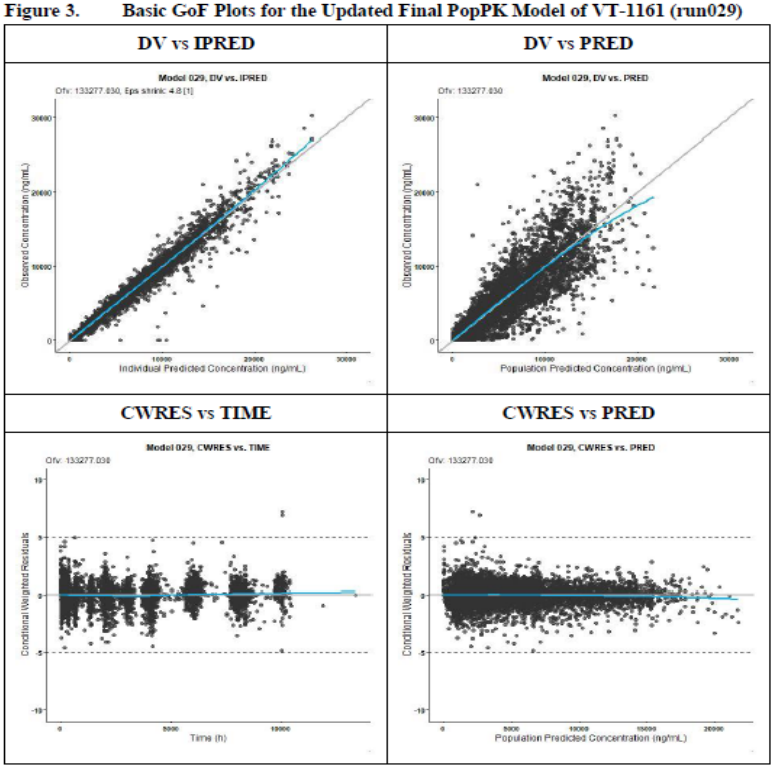
Thirteen Phase 3 subjects were identified as having erroneous values for body weight and height. The final model (run022b) was rerun after making the body weight and height corrections. The updated final model (run029) gave similar results to run022b, with all parameters estimated within a 10% difference except Vp/F, which decreased by 13%. The GoF plots for run022b and run029 were nearly identical. The median t½el was estimated to be 3890 hours (95% CI = 3530 to 4220 hours) based on final model parameters from the nonparametric bootstrap.

Table 5. Parameter Estimates and Bootstrap Results for the Updated Final PopPK Model of VT-1161 (run029)

Parameter (Units)	NONMEM Estimate (%RSE)	Bootstrap Estimate Median (2.5^{th} – 97.5^{th} Percentile)
CL/F (L/h)	0.197 (4.64%)	0.209 (0.168 - 0.291)
Vc/F (L)	631 (4.30%)	612 (430 - 780)
Q/F (L/h)	36.9 (3.99%)	39.1 (30.3 - 53.1)
Vp/F (L)	476 (5.81%)	551 (296 - 1030)
Ka (1/h)	0.508 (15.0%)	0.495 (0.343 - 0.723)
Tlag (h)	0.966 (0.617%)	0.967 (0.938 - 0.997)
Formulation on F (FORM=0 or 2)	1.57 (3.83%) [36% lower F1 for over-encapsulated formulation]	1.67 (1.35 - 2.23)
Formulation on CL/F (FORM=1) [exp(θ)]	0.684 (12.8%) [1.98]	0.642 (0.323 - 0.899)
Additive residual error (ng/mL)	95.2 (2.94%)	93.3 (60.9 - 127)
Proportional residual error (%)	12.2% (1.26%)	12.2% (11.1 - 13.6)
IIV on CL/F (CV%)	68.9% (3.12%)	69.4% (62.7 - 79.6)
IIV on Vc/F (CV%)	39.1% (5.58%)	39.4% (34.0 - 49.8)
IIV on Vp/F (CV%)	156% (3.57%)	147% (46.3 - 203)
IIV on Ka (CV%)	184% (5.41%)	186% (119 - 428)
$t_{½el}$ (hours)[a]	3900 (N/A)	3890 (3530 – 4220)

IIV = Inter-individual variability, reported as a CV%, calculated as sqrt(ω)*100; %RSE = Relative standard error expressed as a percent, calculated as (Standard Error)/(Estimate)*100; %RSEs for IIV are reported on the approximate standard deviation scale, calculated as (Standard Error/Variance Estimate)/2*100.
Formulation: 0 = capsules, 1 = over-encapsulated tablets, 2 = tablets without over-encapsulation.
Expression in [ ] is the model equation and resulting effect size for the covariate effect.
[a] $t_{½el}$ estimate is calculated based on the final model parameter estimates for CL/F, Vc/F, Q/F, and Vp/F (Equation 10 and Equation 11)

Figure 3. Basic GoF Plots for the Updated Final PopPK Model of VT-1161 (run029)

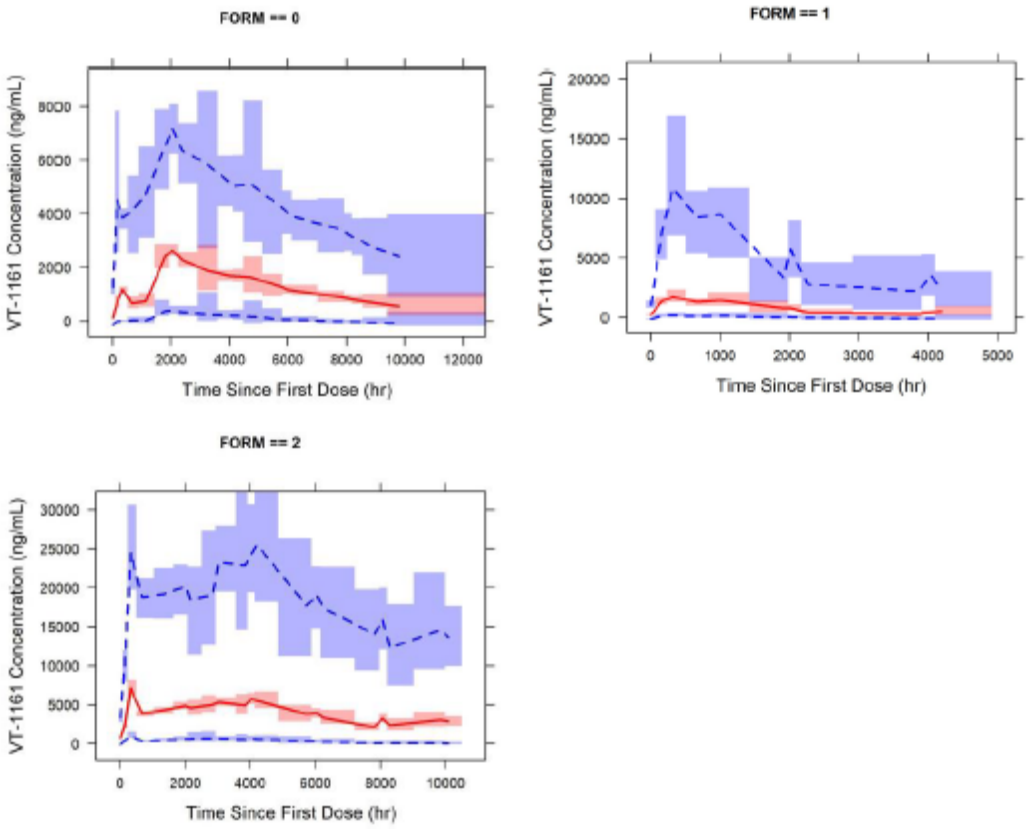


CWRES = Conditional weighted residuals; DV = Observed concentrations; IPRED = Individual predicted concentrations; PRED = Population predicted concentrations

The nonparametric bootstrap estimates for run029 were similar to the NONMEM estimates, and the estimates were contained within the 2.5th to 97.5th percentiles, suggesting good model performance.

Additional model evaluation plots included VPC stratified by formulation. The VPC plots below show that the median, 2.5th, and 97.5th percentile of concentrations over time were well predicted by the model for each formulation studied, as was seen for the original final model (run022b).

Figure 4. Visual Predictive Checks for the Updated Final PopPK Model of VT-1161 (run029) Stratified by Formulation



FORM = Formulation; 0 = Capsules; 1 = Over-encapsulated tablets; 2 = Tablets without over-encapsulation

When VT-1611 was administered in anhydrous micronized form, the capsule and tablet formulations had the same absorption profile (bioavailability and Ka). The X-hydrate non-micronized form of VT-1611 when administered as a capsule did not differ either from the anhydrous micronized formulations (capsule or tablet), for bioavailability, or for Ka. The X-hydrate non-micronized form when administered as an over-encapsulated tablet showed a difference in bioavailability, but it cannot be firmly concluded if this effect is due to the form itself, the tablet formulation, or the over-encapsulation as the X-hydrate non-micronized form was not tested as a simple tablet.

Table 5: Summary of ETA Shrinkage (PopPK report)

Parameter	Shrinkage
IIV on Apparent clearance (CL/F)	15.7 %
IIV on Apparent central volume of distribution (V2/F)	43.8 %
IIV on Apparent peripheral volume of distribution (V3/F)	14.6%
IIV on first order absorption rate (Ka)	57.3%

Applicant's conclusions

- The PK of VT-1161 was adequately described by a 2-compartment model with first-order absorption, an absorption lag time, and first-order elimination.
- Body weight was found to be positively correlated with CL/F, Vc/F, Q/F and Vp/F using fixed allometric exponents of 0.75 for CL/F and Q/F and 1.0 for Vc/F and Vp/F, which corresponds to a

35% lower CL/F and Q/F and 44% lower Vc/F and Vp/F for a 40 kg subject compared to a subject with the median body weight of 71.7 kg.

- Over-encapsulated tablets were correlated with a ~36% lower bioavailability and a ~2x higher CL/F compared to capsules or tablets without over-encapsulation.
- No other covariates were identified to significantly affect the PK of VT-1161.
- The median t½el was estimated to be 3890 hours (95% CI = 3530 to 4220 hours) based on the final model parameters.

Impaired renal function

CL-020 enrolled female subjects with severe renal disease (n=8; ESRD not on haemodialysis) or with normal renal function (n=8). On Day 1, following an appropriate meal for the renally impaired cohort and a standard high fat meal for the normal cohort, each subject received a single oral dose of 600 mg of oteseconazole and samples were collected over 72 h plus samples on Days 11 and 28. The AUC_{0-t} and Cmax oteseconazole were approximately 25% and 31% lower, respectively, in severe renal disease relative to normal renal function.

Table 2.7.2-27. Oteseconazole PK Parameters (CL-020)

PK Parameters	Severe Renal Disease	Normal Renal Function
AUC_{0-t} (ng*hr/mL)	340600 (52.0) [n=8]	456500 (44.0) [n=8]
C_{max} (ng/mL)	1717 (52.1) [n=8]	2493 (44.6) [n=8]
T_{max} (hr)	5.017 (3.00, 6.05) [n=8]	4.000 (3.92, 8.02) [n=8]

Abbreviations: AUC_{0-t}=area under the plasma concentration versus time curve from time 0 to time t; C_{max}=maximum measured plasma concentration; PK=pharmacokinetic; SD=single-dose; T_{max}=time to reach maximum concentration
Note: AUC and C_{max} are presented as geometric mean (geometric CV%); T_{max} is presented as median (minimum, maximum).

There was considerable overlap in individual AUC_{0-t} and Cmax values between subjects in both cohorts with geometric CV% for AUC_{0-t} and Cmax being greater than 44%.

Impaired hepatic function

CL-019 evaluated oteseconazole PK in 17 female subjects with normal hepatic function (C-P score <5) or with moderately impaired hepatic function (C-P score 7-9). All subjects were dosed following a standardized high-fat meal (30% fat) with 600 mg (4 x 150 mg capsules).

Mean AUC_{0-t} and Cmax were approximately 15% higher and 17% lower, respectively, in subjects with moderately impaired hepatic function relative to subjects with normal hepatic function. Mean t½ values were longer in the moderately impaired hepatic function cohort and CL/F values were slower. The mean AUC%extrap was > 70%, suggesting that the terminal elimination phase was not robustly estimated with the 648-hour sampling interval.

Table 11–2 Summary of Plasma VT-1161 Pharmacokinetic Parameters Following the Administration of 600 mg VT-1161 (4 x 150 mg Capsules) in Female Subjects with Normal Hepatic Function and Moderately Impaired Hepatic Function (Pharmacokinetic Population)

Pharmacokinetic Parameters	Normal Hepatic Function	Moderately Impaired Hepatic Function
AUC_{0-t} (ng*hr/mL)	424300 (70.4) [n=8]	487300 (30.8) [n=9]
AUC_{0-inf} (ng*hr/mL)	1512000 (84.9) [n=5]	2846000 (29.9) [n=6]
$AUC_{\%extrap}$ (%)	71.15 (13.2) [n=5]	81.97 (3.0) [n=6]
C_{max} (ng/mL)	1952 (88.7) [n=8]	1622 (37.5) [n=9]
T_{max} (hr)	5.959 (2.97, 11.95) [n=8]	8.000 (2.93, 10.00) [n=9]
$t_{½}$ (hr)	1510.614 ± 530.2757 [n=5]	2350.183 ± 351.4353 [n=6]
λ_z (1/hr)	0.0005157 ± 0.00020928 [n=5]	0.0003003 ± 0.000043729 [n=6]
CL/F (L/hr)	0.5202 ± 0.51242 [n=5]	0.2185 ± 0.064118 [n=6]
V_z/F (L)	996.0 ± 803.30 [n=5]	741.3 ± 235.69 [n=6]

Normal Hepatic Function: 600 mg VT-1161 (4 x 150 mg capsules) administered following high-fat (30%) breakfast in healthy female subjects with normal hepatic function
Moderately Impaired Hepatic Function: 600 mg VT-1161 (4 x 150 mg capsules) administered following high-fat (30%) breakfast in female subjects with moderately impaired hepatic function
AUCs and C_{max} values are presented as geometric mean and (geometric CV%).
T_{max} values are presented as median (minimum, maximum).
Other parameters are presented as arithmetic mean ± SD.
Source: Tables 14.2.1.3 and 14.2.1.4
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Race

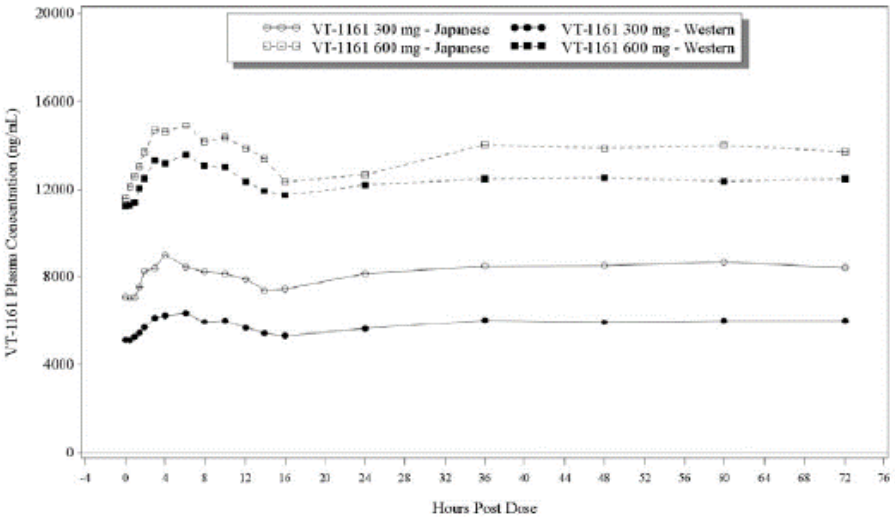
CL-008 compared oteseconazole PK between 25 Japanese and 26 non-Japanese subjects, defined according to 2 parents and 4 grandparents being Japanese or not. Furthermore, the Japanese subjects were to have been born in Japan, to have lived outside Japan for < 10 years and to mainly eat a Japanese style diet. Male and female subjects were aged 18-65 years and resident in the US. Dosing was in 4 cohorts defined by 300 mg or 600 mg QD for 14 days and race. Dosing was after a moderate fat and moderate kcal breakfast.

There were differences in body weights and BMI between cohorts, especially between Japanese and Western subjects that received 300 mg QD, with a lower mean weight and BMI for Japanese subjects.

Characteristic Statistic / Category	VT-1161 300 mg Japanese Subjects (N=13)	VT-1161 300 mg Western Subjects (N=14)	VT-1161 300 mg All Subjects (N=27)	VT-1161 600 mg Japanese Subjects (N=12)	VT-1161 600 mg Western Subjects (N=12)	VT-1161 600 mg All Subjects (N=24)	Overall (N=51)
WEIGHT (kg)							
N	13	14	27	12	12	24	51
Mean	60.25	76.46	68.65	67.29	71.27	69.28	68.95
Standard Deviation	10.278	11.059	13.343	12.947	12.296	12.514	12.834
Median	61.50	78.50	63.60	63.95	69.10	65.75	64.90
Minimum, Maximum	42.3, 86.5	60.7, 94.1	42.3, 94.1	48.8, 98.2	52.8, 98.0	48.8, 98.2	42.3, 98.2
BODY MASS INDEX (kg/m^2)							
N	13	14	27	12	12	24	51
Mean	22.55	26.19	24.44	24.02	24.24	24.13	24.29
Standard Deviation	2.574	2.443	3.079	2.893	2.502	2.648	2.860
Median	22.72	26.15	24.36	23.65	23.40	23.50	23.91
Minimum, Maximum	18.4, 28.1	21.4, 29.9	18.4, 29.9	20.0, 31.9	21.0, 29.5	20.0, 31.9	18.4, 31.9

Differences between ethnic groups in Cmax and AUC_{0-72} were greater after 300 mg vs. 600 mg doses.

Figure 2.7.2-13. Mean Oteseconazole Plasma Concentrations over Time at Day 14 (CL-008)



Cmax and AUC_{0-72} were approximately 40% and 10% higher in Japanese subjects after 300 mg and 600 mg doses, respectively. Median Tmax was at 4 h for Japanese subjects and 6 h for Western subjects regardless of dose. The t1/2 exceeded 1800 h. Total clearance was higher in Japanese subjects after 300 mg but was similar between ethnic groups after 600 mg.

Table 2.7.2-26. Oteseconazole PK Parameters (CL-008)

PK Parameter (unit)	Statistic	Oteseconazole 300 mg		Oteseconazole 600 mg	
		Japanese N=11	Western N=12	Japanese N=11	Western N=12
AUC_{0-72} (ng*hr/mL)	Mean	595427	421434	982018	894336
	CV%	25.7	24.0	31.3	28.0
C_{max} (ng/mL)	Mean	9371	6577	15576	14104
	CV%	22.4	22.6	26.8	29.8
T_{max} (hr)	Median	4.00	6.00	4.00	6.00
	Min, Max	2.0, 24.0	3.0, 10.3	1.5, 12.0	2.0, 10.2
$t_{½}$ (hr)	Mean	1835 [a]	2379	58482	3118 [b]
	CV%	43.0	53.8	310.5	59.0
CL/F (L/hr)	Mean	1.642 [a]	2.332	2.000	2.086 [b]
	CV%	25.6	28.5	27.8	28.8

Abbreviations: AUC_{0-72}=area under the plasma concentration-time curve from 0 to 72 hours; CL/F=apparent oral clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation; max=maximum; min=minimum; PK=pharmacokinetic; $t_{½}$=half-life; T_{max}=time to reach maximum concentration

[a] N=10

[b] N=8

Applicant's sub-group analysis

An analysis was conducted to assess oteseconazole plasma concentration in subgroups defined by age, race, ethnicity, baseline BMI, diabetes and region. It seems that this was based on the observed data collected in Phase 3 studies at weeks 2, 12 and 48. Overall, plasma concentrations were relatively consistent among subgroups for each time point evaluated. Differences in oteseconazole plasma concentrations among subgroups appear to be correlated with Baseline BMI, with concentrations increasing at lower Baseline BMIs.

There were minor differences in oteseconazole mean plasma concentration were observed by race, ethnicity and region except for higher mean plasma concentrations in Asians and Japanese, associated with lower Baseline BMI. Lower oteseconazole plasma concentrations were observed in subjects with diabetes, likely related to a higher BMI in this population.

Drug-drug interactions

Oteseconazole as a victim

- There were two in-vitro studies of the metabolism of oteseconazole, both of which suggested little to no loss of substrate. Incubations with a panel of recombinant human CYP enzymes (50 pmol P450/mL, 120 minutes) indicated that CYP1A2, CYP2C8 and CYP2D6 may be involved in the metabolism of oteseconazole but substrate loss was small (maximum loss of 18%). However, oteseconazole lacks affinity for these enzymes and has high protein binding. As such, if the loss of oteseconazole in the in-vitro study is attributed to metabolism, such metabolism should not be clinically relevant.

- Two transporter studies evaluated whether oteseconazole was a substrate of selected transporters. Results suggested that oteseconazole is not a substrate of P-gp, BCRP, OATP1B1, OATP1B3, OCT2, OAT1 and OAT3.

Oteseconazole as a perpetrator

Results for in-vitro CYP inhibition studies are summarised below.

Enzyme	Enzyme reaction	Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		30-minute preincubation with NADPH		Potential for metabolism-dependent inhibition [c]
		IC_{50} (μM) [a]	Inhibition observed at 10 μM (%) [b]	IC_{50} (μM) [a]	Inhibition observed at 10 μM (%) [b]	IC_{50} (μM) [a]	Inhibition observed at 10 μM (%) [b]	
CYP1A2	Phenacetin *O*-dealkylation	> 10.0	11	> 10.0	16	> 10.0	7.7	No
CYP2B6	Efavirenz 8-hydroxylation	4.0	70	3.9	70	3.8	72	No
CYP2C8	Amodiaquine *N*-dealkylation	1.4	88	2.1	88	1.9	88	No
CYP2C9	Diclofenac 4′-hydroxylation	> 10.0	48	> 10.0	46	> 10.0	47	No
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	9.7	47	> 10.0	52	9.3	52	No
CYP2D6	Dextromethorphan *O*-demethylation	9.4	52	9.2	53	> 10.0	41	No
CYP3A	Testosterone 6β-hydroxylation	9.6	50	> 10.0	50	6.6	56	No
CYP3A	Midazolam 1′-hydroxylation	> 10.0	42	> 10.0	35	> 10.0	43	No

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values
b Inhibition observed (%) is calculated with the following formula (results are rounded to two significant figures):
Inhibition observed (%) = 100% − Percent solvent control
c Metabolism-dependent inhibition was determined by comparison of IC_{50} values both with and without preincubation and with and without NADPH-generating system present in the preincubation, by comparison of the observed inhibition (%) for all preincubation conditions and by visual inspection of the IC_{50} plots

Using a mechanistic static model, there was no indication for in-vivo inhibition of CYP2B6 and CYP2C8 with estimated AUCR < 1.25. Therefore, the applicant did not conduct an in-vivo DDI study with oteseconazole and substrates of CYP2B6 or CYP2C8 is.

Regarding CYP3A, which is an enzyme with significant abundance both in the hepatocytes and the enterocytes, the mechanistic static model considers the GI exposure as well. Since the mechanistic model indicated in-vivo inhibition for CYP3A a clinical DDI study was performed.

Results for in-vitro CYP induction studies are shown below.

Table 2 **Summary of *In Vitro* Induction Response (mRNA Expression) by VT-1161 as an Inducer of Human CYP Enzymes**

Enzyme	E_{max} (fold)[a]	EC_{50} (μM)[a]
CYP1A2[b]	2.06	1.55
CYP2B6[b]	4.26	2.96
CYP2C8[c]	3.21	3.85
CYP2C9[c]	1.24	4.38
CYP2C19[b]	1.97	4.81
CYP3A4[d]	6.10	3.05

a mean values
b n=3; sigmoidal Hill model (n=1) + sigmoid 3-parameter model (n=2)
c n=2; sigmoid 3-parameter model
d n=4: sigmoidal Hill model (n=1) + sigmoid 3-parameter model (n=3)
E_{max} = maximal fold induction *in vitro*; EC_{50} = concentration of inducer associated with half-maximal induction

Results of in-vitro transporter inhibition studies are shown below.

Table 2.7.2-5. In Vitro Inhibition of Human Transporters by Oteseconazole

Transporter	IC_{50} (μM) or % Inhibition
BCRP	0.42
P-gp	2.9
OATP1B1	3.0
OATP1B3	2.6
OAT1	<15% at 25 μM
OAT3	46% at 25 μM
OCT2	<15% at 25 μM

Abbreviations: BCRP=breast cancer resistance protein; IC_{50}=half-maximal inhibitory concentration; OAT=organic anion transporter; OCT=organic cation transporter; P-gp=p-glycoprotein; OATPB= organic anion-transporting polypeptide B
Source: XT148002

CL-007 evaluated the effect of single and multiple doses of oteseconazole on the PK of midazolam. In the DDI cohort 28 subjects received 2 mg oral midazolam on Day 1, followed by 600 mg (4x150 mg tablets) QD oteseconazole on Days 3-16. Further 2 mg midazolam doses were co-administered with oteseconazole on Days 3 and 16. All dosing was after a high kcal and high fat breakfast.

Oteseconazole plasma exposure increased from Day 3 to Day 16, reflecting the long elimination $t_{1/2}$. Using an ANOVA model and a mixed model with repeated measures to calculate GLS means ratios and 90% CIs, the 90% CIs around the AUC ratios did not fall within the 0.8 to 1.25 interval on Day 16. Overall co-administration with oteseconazole led to reduced plasma exposures to midazolam.

Table 11: Relative Bioavailability of Midazolam as Assessed by Geometric Least Squares Mean Ratios and 90% Confidence Intervals

Midazolam PK Parameter	Day3/Day 1 Ratio (90% CI)	Day 16/Day 1 Ratio (90% CI)
ANOVA Model*		
C_{max} (ng/mL)	1.30 (1.12 – 1.52)	0.97 (0.83 – 1.14)
AUC_{24} (h*ng/mL)	0.86 (0.73 – 1.01)	0.64 (0.54 – 0.75)
AUC_{inf} (h*ng/mL)	0.85 (0.72 – 1.00)	0.63 (0.53 – 0.75)
Mixed Model For Repeated Measures^		
C_{max} (ng/mL)	1.30 (1.18 – 1.44)	0.94 (0.83 – 1.08)
AUC_{24} (h*ng/mL)	0.86 (0.83 – 0.90)	0.623 (0.58 – 0.67)
AUC_{inf} (h*ng/mL)	0.85 (0.82 – 0.89)	0.617 (0.57 – 0.67)

Source: Tables 14.2.3 and 14.2.3a.

* The first three rows show the GLS means, ratios, and CIs from an ANOVA model with log-transformed PK parameter as the outcome and sampling day as fixed effects.

^ The last three rows show the GLS means, ratios, and CIs from mixed model for repeated measures with log-transformed PK parameter as the outcome with sampling day as categorical time variable. Kenward-Roger correction for the denominator degree of freedom was used and unstructured covariance matrix was assumed. The mixed model for repeated measures was used as a sensitivity analysis for the ANOVA model.

CL-014 evaluated a single oral dose of an OC (35 µg ethinyl oestradiol and 1 mg norethindrone) given alone on Day 1 and given with oteseconazole on Day 21, this being the last day of dosing with 150 mg/day from Days 8-21. There were 24 women enrolled aged from 19-65 years (mean 46 years). Mean oteseconazole trough concentrations increased with number of dosing days. The maximum mean concentration (3206 ng/mL) was observed at 480 h (Day 21 pre-dose).

Based on the GMRs, mean plasma EE Cmax, AUC_{0-t} and $AUC_{0-\infty}$ were 12% to 20% higher after co-administration on Day 21 compared to Day 1. Estimates of intra-subject CV% were 12%, 13%, and 26% for AUC_{0-t}, $AUC_{0-\infty}$ and Cmax, respectively.

Table 11–3 Summary of Statistical Comparisons of Plasma Ethinyl Estradiol Pharmacokinetic Parameters Following the Administration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone Alone on Day 1 or Coadministration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone with Multiple Doses of 150 mg VT-1161 on Day 21 (PK Population)

	MD VT-1161 + SD EE/NE (Test)		EE/NE Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC_{0-t} (pg*hr/mL)	939.3	24	835.4	24	112.43	106.19 - 119.04	11.58
AUC_{0-inf} (pg*hr/mL)	1136	24	1006	24	112.98	105.86 - 120.58	13.21
C_{max} (pg/mL)	65.53	24	54.48	24	120.29	106.05 - 136.44	25.89

Based on the GMRs, there was no effect of co-administration on NE. However, the 90% CI around the ratios for calculated AUCs did not span 1.00, indicating a small decrease in exposures on co-administration. Estimates of intra-subject CV% were 11% for AUC_{0-t} and $AUC_{0-\infty}$ and 37% for Cmax.

Table 11–5 Summary of Statistical Comparisons of Plasma Norethindrone Pharmacokinetic Parameters Following the Administration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone Alone on Day 1 or Coadministration of a Single Dose of 35 µg Ethinyl Estradiol/1 mg Norethindrone with Multiple Doses of 150 mg VT-1161 on Day 21 (PK Population)

	MD VT-1161 + SD EE/NE (Test)		EE/NE Alone (Reference)				
Parameter	Geometric LSM	n	Geometric LSM	n	GMR (%)	90% Confidence Interval	Intra-subject CV%
AUC_{0-t} (pg*hr/mL)	53120	24	56960	24	93.25	88.26 - 98.53	11.16
AUC_{0-inf} (pg*hr/mL)	56020	24	59760	24	93.74	88.61 - 99.17	11.41
C_{max} (pg/mL)	6247	24	6472	24	96.52	80.87 - 115.19	36.92

CL-015 was conducted in 48 healthy adult female subjects aged 21-65 years in 2 cohorts:
Digoxin Cohort - 0.5 mg digoxin on Days 1, 3 and 16 and oteseconazole 150 mg QD on Days 3-16
Rosuvastatin Cohort - 20 mg rosuvastatin QD on Days 1, 3 and 16 and oteseconazole 150 mg QD on Days 3-16.
All dosing was after a high-fat, high-calorie meal. Digoxin and rosuvastatin Day 3 data were baseline adjusted due to measurable pre-dose plasma concentrations of >5% of Day 3 Cmax in 23/23 and 7/23 subjects in respective cohorts.

Oteseconazole Cmax, AUC_{0-24} and AUC_{0-t} were 4 to >8 times higher on day 16 (MD) vs. Day 3 (SD) due to expected accumulation, which is evident from the serial trough concentrations.

Digoxin Cmax and AUC_{0-24} were not affected by oteseconazole on Day 3 or 16.

Rosuvastatin mean Cmax and AUC_{0-24} were 85 to 87% higher following co-administration on Day 3 and 114 to 118% higher following co-administration on Day 16 vs. rosuvastatin alone.

Table 2.7.2-24. Rosuvastatin PK Parameters – Summary of Statistical Comparison (CL-015)

	Oteseconazole + Rosuvastatin (Test)		Rosuvastatin Alone (Reference)				
PK Parameter	Geo LSM	n	Geo LSM	n	GMR (%)	90% CI	Intra-subject CV%
Oteseconazole – Single Dose							
AUC_{0-24} (ng*hr/mL)	66.19	24	35.88	24	184.49	169.06 -201.32	18.17
$AUC_{0-\infty}$ (ng*hr/mL)	89.41	17	48.03	20	186.15	167.41 – 207.00	18.37
C_{max} (ng/mL)	7.424	24	3.971	24	186.94	167.62 – 208.50	22.81
Oteseconazole – Multiple Doses							
AUC_{0-24} (ng*hr/mL)	76.81	24	35.88	24	214.10	196.60 – 233.15	17.73
$AUC_{0-\infty}$ (ng*hr/mL)	93.03	24	48.05	20	193.63	175.80 – 213.27	18.53
C_{max} (ng/mL)	8.657	24	3.971	24	217.99	196.00 – 242.44	22.21

3.3.1.2. Pharmacodynamics

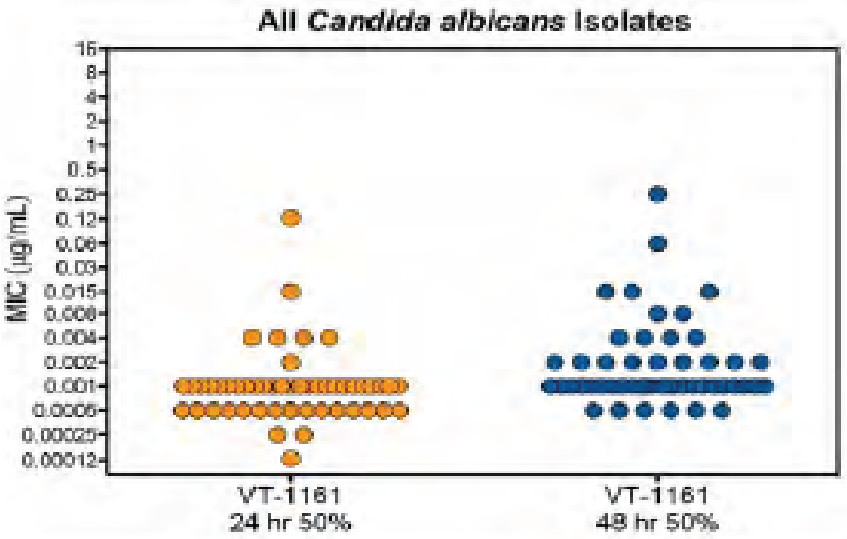
Mechanism of action

Lanosterol demethylase (cytochrome P450 [CYP] 51), an enzyme essential for fungal growth, catalyses an early step in the biosynthetic pathway of ergosterol, a sterol required for fungal cell membrane formation and integrity. The currently approved azole drugs contain an imidazole or triazole ring system that binds tightly to the catalytic haem-iron of fungal CYP51 as well as to the haem-iron of many mammalian CYP enzymes. Inhibition of fungal CYP51 by azole antifungal agents results in the accumulation of 14-methylated sterols, some of which are toxic to the fungus.

Oteseconazole (VT-1161) differs from the approved azole antifungal agents in having a tetrazole group (4 N and 1C atoms). It has relatively high affinity for fungal CYP51 and relatively low affinity for mammalian CYP51. The oteseconazole IC_{50} for fungal CYP51 was 1.5 µM whereas human CYP51 was not inhibited by 50 µM oteseconazole as determined in a sensitive spectrophotometric assay.

In-vitro activity against Candida species

In **VMT-UTHSCSA-19**, using the CLSI M27-A3 methodology, the in-vitro activity of oteseconazole was determined for 50 recent clinical isolates of *C. albicans* submitted to a US reference laboratory. Oteseconazole MICs were <0.5 mg/L and similar for isolates with fluconazole MICs <1 and ≥ 1 mg/L. There was little or no difference in in-vitro activity when determined after 24 h or 48 h incubation.



In **VMT-UTHSCSA-13**, the activity of oteseconazole (reading at 50% growth inhibition) was determined against *C. albicans* with resistant to fluconazole and/or voriconazole or to echinocandins.

Isolate #	Mechanism of Resistance
6482	Unknown mechanism of azole resistance
53264	FKS1 point mutation
CLY719	FKS1 point mutation; unknown mechanism of azole resistance
2274	ERG11 point mutation S405F
6431	No FKS1 point mutation; unknown mechanism of azole resistance
1649	Wild-type
2440	ERG11 Point mutation V437I & over-expression of MDR1 & ERG11
2307	ERG11 point mutation K128T & over-expression of CDR1, CDR2, & ERG11
412	Wild-type control for 2307
3795	ERG11 point mutation
1002	Wild-type control for 3034
3034	Over-expression of CDR1, CDR2, & MDR1
4018	Wild-type
SC5314	Wild-type (genome available)
2257	ERG11 point mutation S405F
43001	FKS1 point mutation; unknown mechanism of azole resistance
4254	FKS1 point mutation
4380	ERG11 point mutation V437I & over-expression of CDR1, CDR2, & ERG11
42379	FKS1 point mutation; unknown mechanism of azole resistance

MIC_{50} values of oteseconazole were the same or mostly within one doubling dilution regardless of time of incubation (24 h or 48 h). The highest oteseconazole MIC_{50} values were observed for three strains that showed reduced susceptibility to fluconazole and to voriconazole. Strains that only showed reduced susceptibility to fluconazole were inhibited at 0.06 mg/L or less of oteseconazole. None of the strains tested had caspofungin MICs that would classify them as resistant.

In **VMT-CDC-1**, also using CLSI methodology, MIC_{50} values of oteseconazole were determined against 100 *C. auris* isolates collected worldwide, including representation from four clades. The overall results are shown in the table below according to fluconazole susceptibility. Oteseconazole activity was not markedly affected by resistance to fluconazole. The MICs were rather variable across clades, perhaps partly influenced by difficulty reading endpoints because of trailing growth. MIC_{90} values were 8 mg/L for clade 1, 0.25 mg/L for clade 2, 0.5 mg/L for clade 3 and 1 mg/L for clade 4.

Table 4. MIC data for fluconazole resistant vs. susceptible isolates

	Minimum Inhibitory Concentration (µg/ml)	
Fluconazole Interpretation	Susceptible	Resistant
No. Isolates	30	69
Range	≤0.016 - 8	0.125 - 8
Mode	0.5	1
MIC_{50}	0.5	1
MIC_{90}	1	4

In a published study by **Nishimoto *et al.*** (*Antimicrob Agents Chemother* 2019;63; e00341) MICs were determined against 68 *C. albicans*, including isolates with specific types of mutational azole resistance. The oteseconazole geometric mean MIC was ≤0.15 µg/ml against predominantly fluconazole-resistant (≥8 µg/ml) isolates. However, 5/68 isolates exhibited MICs >2 µg/ml.

Table 2.7.2-32. Oteseconazole and Fluconazole MICs against 68 Clinical Isolates of *C. albicans* Characterized for Azole Resistance

Antifungal	MIC, µg/mL			
	Range	Geomean	MIC_{50}	MIC_{90}
Oteseconazole	≤0.015 - >8	0.15	0.12	1
Fluconazole	≤0.12 - >64	20	32	>64

Oteseconazole MICs were higher compared to the control strain (SC5314) for hyperactive Tac1 strains and two strains with Erg11 substitutions but showed activity against hyperactive Mrr1 and Upc2 strains. While mutations affecting Erg3 activity appear to greatly reduce susceptibility to oteseconazole, the higher MICs observed for 4 isolates could not be explained by known azole resistance mechanisms, suggesting the presence of undescribed resistance mechanisms.

In a published study by **Schell *et al*.** (*Antimicrob Agents Chemother* 2017;61; e01817) oteseconazole MICs were determined for 34 *C. glabrata* and 50 *C. krusei* isolated from the blood. All *C. glabrata* isolates contained FKS gene mutations and most were resistant to echinocandins and fluconazole. Oteseconazole inhibited 90% of these 84 isolates at ≤ 1 mg/L and most were inhibited at ≤ 0.25 mg/L.

Table 2.7.2-35. Oteseconazole, Fluconazole, and Anidulofungin MICs against *C. glabrata* and *C. krusei* Clinical Isolates from Patients with Candidemia

Candida spp.	Antifungal	MIC, µg/mL			
		Range	Geomean	MIC_{50}	MIC_{90}
C. krusei (50 isolates)	Oteseconazole	≤0.015 - 1	0.16	0.25	0.5
	Fluconazole	16 - 128	34	32	64
	Anidulofungin	≤0.015 - 0.25	0.03	0.03	0.03
C. glabrata (34 isolates)	Oteseconazole	≤0.015 - 1	0.16	0.12	1
	Fluconazole	1 - 128	5.2	2	64
	Anidulofungin	0.06 - 8	0.92	1	8

CL-018 was a TQT study conducted in 59 healthy female subjects (56 completed) aged 19-62 years who were randomised into 3 cohorts with a 2:1:1 ratio:
Cohort 1 (Active Treatment Arm)
Oteseconazole 600 mg QD on Days 1–13 and 1200 mg on Day 14
Cohort 2A Control (Moxifloxacin/Placebo)
Moxifloxacin 400 mg on Day 1
Cohort 2B Control (Placebo/Moxifloxacin)
Moxifloxacin 400 mg on Day 15

Geometric mean oteseconazole AUC_{0-24} and Cmax on Day 14 were 18.4- and 12.5-fold higher, respectively, compared to AUC_{0-t} and Cmax on Day 1 and 3.9- and 3.8-fold higher vs. Day 4. The post 1200 mg (Day 14) mean Cmax was 13,150 ng/mL (range 7,370 to 21,100 ng/mL), which was slightly higher than the target supratherapeutic exposure of 10,000 ng/mL. A concentration-QTc analysis for moxifloxacin showed that the slope of the relationship was positive and statistically significant. The lower bound of the 2-sided CI of the predicted QT effect (17.59 msec [90% CI: 12.51 to 22.67]) at the geometric mean peak moxifloxacin concentration (2439.3 ng/mL) was above 5 msec, demonstrating assay sensitivity.

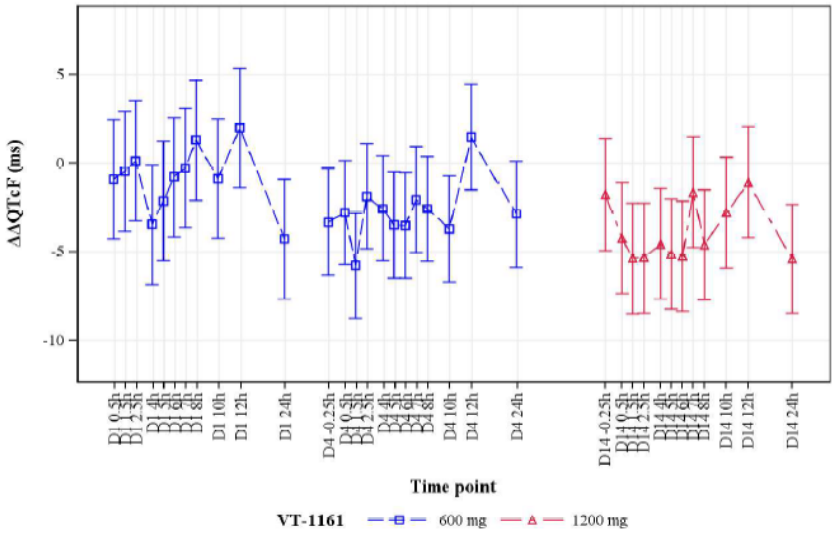
The analysis of those given oteseconazole showed that ECG parameters were generally within normal limits at each ECG time point. There were no subjects with QTcF intervals > 500 msec in any cohort.

QTcF change from baseline ≥ 30 msec to < 60 msec

- In Cohort 1, 3/26 exhibited a change ≥ 30 msec to < 60 msec.
- In Cohort 2A, 1/15 exhibited a change ≥ 30 to < 60 msec.
- In Cohort 2B, 3/15 had a change ≥ 30 msec to < 60 msec and one had a change of 60 msec on Day 15.

In the results by time point analysis, the pattern across doses and post-dose time points suggested a small and not clinically relevant shortening of LS mean ΔΔQTcF.

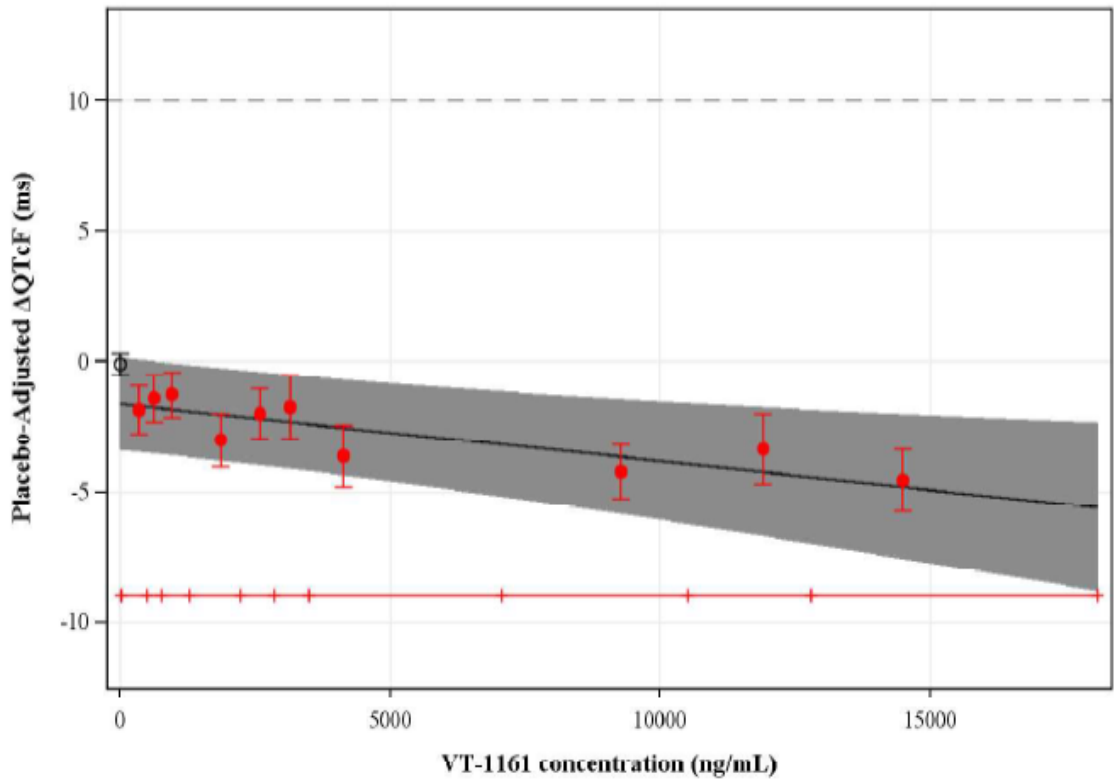
Figure 14.2.5.1 Placebo-corrected change-from-baseline QTcF (ΔΔQTcF) across time point for active analysis (QT/QTc population)



LS mean and 90% CI based on a linear mixed-effects model: ΔQTcF = Treatment + Time + Treatment×Time. A compound symmetry covariance structure was used to specify the repeated measures (time within subject).

At the geometric mean Cmax on Day 14 (12550 ng/mL), the predicted effect on ΔΔQTcF was −4.40 msec (90% CI: −6.95 to −1.86), i.e. a slight shortening of the QTcF interval at supratherapeutic plasma concentrations. Thus, a QTcF prolongation effect (ΔΔQTcF) exceeding 10 msec was excluded within the observed range of oteseconazole plasma concentrations up to 18100 ng/mL.

Figure 14.2.12.1 Model-predicted ΔΔQTc (mean and 90% CI) and estimated placebo-adjusted ΔQTc (mean and 90% CI) across deciles of VT-1161 plasma concentrations (PK/QTc population)



The solid black line with gray shaded area denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF (ms) = −1.65 (ms) - 0.00022 (ms per ng/mL) × VT-1161 plasma concentration (ng/mL).
The red filled circles with vertical bars denote the estimated mean placebo-adjusted ΔQTcF (ΔΔQTcF) with 90% CI displayed at the associated median plasma concentration within each decile for VT-1161, among which the individually estimated placebo-adjusted ΔQTcFi,k (ΔΔQTcFi,k) equals the individual ΔQTcFi,k for subject i administered with VT-1161 at time point k minus the estimation of time effect at time point k. The black circle with vertical bars denotes the mean placebo-adjusted ΔQTcF with 90% CI for placebo at a concentration of 0.
The horizontal red line with notches shows the range of concentrations divided into deciles for VT-1161. The area between each decile represents the point at which 10% of the data are present; the first notch to second notch denotes the first 10% of the data, the second notch to third notch denotes the 10-20% of the data and so on.

The applicant concluded that oteseconazole at plasma levels up to ~18,000 ng/mL, which is >5x the anticipated clinical exposure in routine use, had no clinically relevant effect on QTcF or on HR, PR interval and QRS duration.

3.3.2. Discussion on clinical pharmacology

Pharmacokinetics

General comment on oteseconazole PK

The absolute bioavailability of oteseconazole in humans after oral dosing has not been established due to lack of an IV preparation for clinical use. An attempt to estimate absolute bioavailability in beagle dogs did not yield interpretable results in that absolute bioavailability ranged from 45 to 170% for the 0.5% carboxymethyl cellulose (CMC) formulation and 48 to 209% for the Labrasol formulation.

Oteseconazole is relatively slowly absorbed with a lag time of 0.5 to 2 h to reach the systemic circulation and Tmax typically occurs at ~6 h. After single doses, Cmax increased in a less than dose-proportional fashion whereas AUC increased in proportion to dose. After multiple daily dosing, the oteseconazole Cmax and AUC_{0-24} increase in a nearly dose-proportional fashion up to 320 mg QD. There was significant accumulation in plasma over 7 days of dosing with accumulation ratios based on comparing AUC_T values in the range 4.46 to 6.16 and greatest at the highest dose levels.

The estimates of volume if distribution have been large, suggesting that oteseconazole distributes extensively into tissues. Furthermore, oteseconazole shows >99% binding to plasma proteins.

The in-vitro studies and mass balance study (CL-016) suggest that there is no significant metabolism of oteseconazole in humans. In CL-016, metabolite identification in plasma samples was not performed because unchanged parent drug represented 97% of the radioactivity recovered in the 0–408h plasma extract (based on HPLC-UV retention times).

The terminal elimination phase is very long and it was likely under-estimated in several early studies, because sampling did not continue for long enough and due to limited accuracy of the estimation method. In the mass balance study, the last sampling point was at 6624 hours [276 days] after a single oral dose of 600 mg. It was estimated that ~56% of the radiolabelled dose was recovered in faeces and ~26% was recovered in urine during the 0-278 day period. The mean terminal phase t½ was estimated at 2114 h [88 days] for unchanged oteseconazole. Moreover, the final POPPK analysis estimated the median t½ to be 3890 h [162 days] (95% CI: 3530 – 4220 h). The FDA considerations related to the long terminal elimination half-life have applied a median of approximately 138 days.

Effect of food

The effect of food on oteseconazole PK was initially studied in CL-001 after a single 320 mg dose administered as Phase 1 capsules (delivered as 20 mg and 60 mg sizes). Taking this dose after a standard high-fat meal increased Cmax by 3-fold and $AUC_{0-\infty}$ by 4-fold. However, the effect of food was much less when a 150 mg single dose was administered as a Phase 3 capsule in the formal food effect study (CL-013). In this study, there were 45% and 36% higher Cmax and AUC_{0-72} values, respectively, when dosing followed a high fat and kcal meal. Moreover, Cmax was only 17% higher and there were comparable AUC_{0-72} values when dosing followed a low fat and kcal meal.

The applicant ascribes the discrepancy between studies to the difference between the unmicronised oteseconazole in Phase 1 capsules vs. micronised oteseconazole in Phase 3 capsules, which are intended for commercial use. Therefore, it is notable that in CL-001 the mean Cmax after a 320 mg dose in the fasted state was 338 ng/mL whereas in CL-013 the mean Cmax after a 150 mg dose in the fasted state was 538 ng/mL. This comparison supports a conclusion that the differences in formulation between Phase 1 and Phase 3 capsules had a marked effect on oteseconazole PK.

Importantly, dosing in Phase 2 (using tablets) and 3 (using Phase 3 hard capsules) in women with RVVC was within 30 min after a meal but the exact nature of the meal was not specified. The SmPC recommends dosing with food without any specifications, which is acceptable.

Commercial formulation 150 mg hard capsules

There was no formal assessment of bioequivalence. Study CL013 compared the bioavailability of oteseconazole after dosing with the 150 mg tablet used in the Phase 2 RVVC dose-finding study CL-006 and the 150 mg hard capsule used in the three Phase 3 studies.

Mean plasma concentrations were slightly higher with the tablet until 4 h post-dose but lower from 6h onwards so that AUC_{0-72} was about 13% higher following the capsule formulation. Tmax and mean Cmax values were similar. The findings suggest that CL-006 would not have over-estimated the efficacy of oteseconazole.

The Phase 3 studies used the 150 mg hard capsules as intended for commercial use except that manufacture will occur at a different facility. To support this, the applicant provides results from a bioequivalence study (RGL-004-002) that compared oteseconazole PK over 72 h after dosing in the fed state. Due to the estimated CV%, this was a large study (n=340). The results using the PMRI assay suggested slightly lower bioavailability for oteseconazole from the facility 1 vs. facility 2 capsules. That is, while the 90% CI fell within [80, 125%], so that bioequivalence criteria were met after single doses, the GMRs were 90 and the upper bound was less than 1.00 (~94%). Noting the accumulation that occurs in plasma, it seems unlikely that there would be clinically important differences between formulations in oteseconazole plasma concentrations at steady state.

Oteseconazole PK in subgroups

Renal and hepatic impairment

In CL-020, in which a single oral dose of 600 mg oteseconazole was administered to female subjects, the mean AUC_{0-t} and C_{max} were approximately 25% to 31% lower in those with severe renal disease vs. subjects with normal renal function. The SmPC states that oteseconazole is not recommended in subjects with severe renal impairment.

In CL-019, after a single dose of 600 mg in female subjects, Mean AUC_{0-t} and Cmax were approximately 15% higher and 17% lower, respectively, in subjects with moderately impaired hepatic function relative to subjects with normal hepatic function. Mean t½ values were longer in the moderately impaired hepatic function cohort and CL/F values were slower. The results suggest that no dose adjustment is necessary for subjects with moderate hepatic impairment on grounds of safety or efficacy. In the absence of data and with higher plasma exposures (AUCs) in those with moderate impairment, use in severe hepatic impairment is not recommended.

Other factors

The most important of the factors examined was BMI, with higher concentrations at lower BMI values and *vice versa*. It was thought that differences in weight, and thus BMI, were likely responsible for the higher mean plasma concentrations noted in Asians and Japanese (generally lower BMI) and lower mean plasma concentrations in subjects with diabetes (generally higher BMI). This conclusion is supported by results of CL-008, in which there was a much greater difference in weights between the Japanese and Western subjects who received 300 mg vs. those who received 600 mg, each given daily for 14 days. Cmax and AUC_{0-72} were approximately 40% and 10% higher in Japanese subjects after 300 mg and 600 mg doses, respectively. It is further supported by the observed plasma concentrations in studies CL-011 and -012 vs. CL-017, where the lower mean concentrations in Cl-017 are likely best explained by the higher mean weight and BMI values.

The effect of weight/BMI has potential implications for efficacy (at highest weight/BMI) and safety (at lowest weight/BMI). The applicant's summaries of safety and efficacy examined the effect of BMI and indicated that there was no apparent effect of BMI on the safety profile nor was there an effect on efficacy in prevention of recurrence even in those with BMI ≥ 30 mg/m^2.

POPPK analyses

The conclusions of the final analysis, after inclusion of the Phase 3 PK data, were similar to those of the initial analysis. The final model was a 2-compartment model with first-order absorption, an absorption lag time, and first-order elimination. Body weight was found to be positively correlated with CL/F, Vc/F, Q/F and Vp/F using fixed allometric exponents of 0.75 for CL/F and Q/F and 1.0 for Vc/F and Vp/F. The model predicted a 35% lower CL/F and Q/F and 44% lower Vc/F and Vp/F for a 40 kg subject compared to a subject with the median body weight of 71.7 kg. The over-encapsulated tablet formulation was correlated with lower bioavailability (F) and higher CL/F compared to capsules or tablets without over-encapsulation. No other covariates were identified to significantly affect the PK of oteseconazole.

The final model parameters were estimated with good precision (all RSEs ≤15%) and all parameter estimates were contained within the 2.5th to 97.5th percentiles of the bootstrap results, suggesting good model performance. IIV of PK parameters for the final model was moderate to high (39.1% to 184%). ETA shrinkage for the IIV of Vc/F and Ka (43.8% and 57.3%, respectively) was high, which is likely due to the large proportion of subjects in the analysis with only sparse PK sampling data.

When oteseconazole was administered in anhydrous micronised form, the capsule and tablet formulations had the same absorption profile (bioavailability and Ka). The X-hydrate non-micronized form of VT-1611 when administered as a capsule did not differ either from the anhydrous micronized formulations (capsule or tablet), for bioavailability, or for Ka. The X-hydrate non-micronized form when administered as an over-encapsulated tablet showed a difference in bioavailability, but it cannot be firmly concluded if this effect is due to the form itself, the tablet formulation, or the over-encapsulation as the X-hydrate non-micronized form was not tested as a simple tablet.

Drug-drug interactions

The molecular weight of oteseconazole is 527.4 g/mol, which means that 1 M is 527 g/L and 1 µM is 527 µg/L. Many of the in-vitro studies used concentration up to 10 µM, which is 5270 µg/L (or 5.27 µg/mL). The mean plasma oteseconazole at end of treatment (so reflecting accumulation with repeat dosing) was between ~2.7 µg/mL in CL-017 and ~3.6 µg/mL in CL-012. After a single 600 mg dose in CL-020, the mean Cmax in subjects with normal renal function was ~2.5 µg/mL.

However, oteseconazole is >99% protein bound so the free fraction at end of treatment could be estimated at somewhere between 0.027-0.036 µg/mL. On this basis, the in-vitro studies (some of which used up to 200 µM) used adequate drug concentrations.

In-vitro studies supported a conclusion that oteseconazole is little metabolised after oral dosing in humans, suggesting it is unlikely to be a victim of CYP-mediated drug-drug interactions. Moreover, it does not seem to be a substrate for any of the transporters studied and the range of transporters used seems sufficient in light of the general PK properties of oteseconazole.

The in-vitro studies suggested that oteseconazole is unlikely to exert significant inhibition or induction of CYP isoenzymes or inhibition of the majority of transporters at clinically relevant plasma concentrations. The potential for inhibition of BCRP could not be ruled out. While the applicant used the FDA criteria to determine the need for clinical studies, those conducted were appropriate given the in-vitro data and the target population for oteseconazole.

The effect of oteseconazole on rosuvastatin and digoxin (not the most sensitive P-gp substrate) was assessed after two weeks dosing with oteseconazole 150 mg QD, which was appropriate. There was no appreciable effect of oteseconazole on digoxin.

Given the in-vitro data, it seems that the effect on rosuvastatin was mediated via inhibition of BCRP and not via inhibition of OATP1B, with a >2-fold increase in rosuvastatin Cmax and AUC_{0-24} on co-administration. At this magnitude of effect, a contraindication for co-administration with rosuvastatin would not be considered necessary. It suffices that caution should be applied on co-administration with sensitive substrates of BCRP and that dose adjustment should be considered.

The applicant's decision to conduct a study of co-administration with a COC was appropriate. A design in which single doses of a COC were given before and on completion of a 2-week course of oteseconazole 150 mg QD is acceptable. The findings do not suggest that a clinically significant interaction will occur on co-administration with COCs.

The study with midazolam used 4x150 mg tablets to deliver 600 mg QD for 14 days, taken after a high fat and kcal meal. At this supratherapeutic dose, the midazolam Cmax was unaffected by co-administration. The midazolam AUC_{24} and AUC_{inf} were slightly lower on Day 3 (with the first oteseconazole dose of 600 mg) and markedly lower on day 16 (with the last oteseconazole dose of 600 mg QD). This finding suggests that at 600 mg QD, oteseconazole has some induction effect on CYP3A. After accounting for protein binding, it seems somewhat unlikely that oteseconazole when used at the recommended dose will exert a clinically important reduction in plasma midazolam.

Implications of the very long elimination half-life

Risk of hypersensitivity

Presently, there is currently limited data to address the potential for cross-hypersensitivity between the triazole and imidazole agents and oteseconazole. It is not possible to substantiate that cross-hypersensitivity would not occur. In light of the very long half-life of oteseconazole, the applicant agreed to contraindicate oteseconazole in persons with hypersensitivity to the active substance, to any imidazole or triazole antifungal agent or to any of the excipients.

Proposed duration of contraception and avoidance of breastfeeding

Regarding the indication statement, the applicant accepted the need to confine use to women with no child-bearing potential. Regarding women who still have a potential to become pregnant via any type of assisted reproduction, it is completely unacceptable that the applicant still tries to set a limit for the time after receipt of oteseconazole by including the following contraindication: *Women of non-childbearing potential who have declared intention to use any means of assisted reproduction (including use of stored eggs/embryos or use of donor eggs) within 2 years and 8 months from the start of the treatment.* The only safe way to allow use of oteseconazole in women who could become pregnant by any means is to contraindicate use with no time limit set on the contraindication.

Pharmacodynamics

In common with the licensed azole antifungal agents, the tetrazole compound oteseconazole inhibits the fungal lanosterol demethylase (CYP51). In-vitro data do suggest that it is more selective for the fungal rather than mammalian enzyme (see the Nonclinical Assessment Report for details).

In-vitro susceptibility and resistance

Oteseconazole has in-vitro activity against a range of fungi, but this application concerns only its activity against organisms of the genus Candida. In this genus, *C. albicans* is the predominant species linked to AVVC and RVVC. Generally, *C. glabrata* is now considered to be the second leading cause of RVVC, although *C. tropicalis*, *C. krusei*, *C. parapsilosis* and *C. guilliermondii* may also be causative. The applicant has generated in-vitro data suggesting that oteseconazole may retain activity against some strains that have reduced susceptibility or resistance to fluconazole.

C. krusei is not susceptible to fluconazole due to poor binding affinity to the CYP51 in this species. Acquired resistance to fluconazole among Candida is variable by species, region, type of patient (e.g. immunocompetent or immunosuppressed) and type of infection. For example, the US CDC finds that ~7% of blood culture isolates of Candida species are now resistant to fluconazole (perhaps to some extent driven by increasing prevalence of *C. auris*, which is much more likely to be resistant than other species). In contrast, estimates for resistance to fluconazole in vulvovaginal *C. albicans* are ~0.5-<2% in the US. Moreover, some studies have reported rates for clinical resistance rather than resistance based on MICs and not all studies have characterised the mechanism(s) of resistance to fluconazole.

There are several known mechanisms of resistance to fluconazole and they vary by species. Generally, overexpression of target (ERG11 and UPC2), alteration of target (ERG11), bypass pathways (ERG3) and efflux pump over-expression (various genes may be involved) have all been described.

In this regard, there are some data from VMT-UTHSCSA-13 on oteseconazole in-vitro activity against *C. albicans* with documented resistance to one or more other antifungal agents, including some for which the mechanism involved was known. Since resistance to echinocandins does not affect susceptibility to azole antifungal agents, the strains of most interest were those with reduced susceptibility/resistance to azoles. The highest oteseconazole MIC_{50} values (0.5 mg/L) were observed for three strains that showed reduced susceptibility to fluconazole and to voriconazole. Strains that only showed reduced susceptibility to fluconazole were inhibited at 0.06 mg/L or less of oteseconazole. In a further study (VMT-CDC-1), oteseconazole MICs up to 8 mg/L were documented against a collection of *C. auris* isolates with variable susceptibility to fluconazole. Furthermore, published studies have described oteseconazole MICs ≥8 mg/L for certain strains.

Effect on the QTc interval

The applicant conducted study CL-018 with a maximum dose of 1200 mg oteseconazole (i.e. twice the initial loading dose) administered after 14 daily doses of 600 mg. With the anticipated accumulation in plasma, the mean Cmax values on Days 1 and 4 were 1053 ng/mL and 3441 ng/mL, respectively. The post 1200 mg (Day 14) mean Cmax was 13,150 ng/mL (range 7,370 to 21,100 ng/mL), which was slightly higher than the target supratherapeutic exposure of 10,000 ng/mL.

At the geometric mean Cmax on Day 14 (12550 ng/mL), the predicted effect on ΔΔQTcF was −4.40 msec (90% CI: −6.95 to −1.86), i.e. a slight shortening of the QTcF interval at supratherapeutic plasma concentrations. Thus, a QTcF prolongation effect (ΔΔQTcF) exceeding 10 msec was excluded within the observed range of oteseconazole plasma concentrations.

3.3.3. Conclusions on clinical pharmacology

The very long terminal elimination half-life of oteseconazole, when viewed in conjunction with the nonclinical effects, led to a revised indication that restricts use to women who have no childbearing potential.

The very long terminal elimination half-life of oteseconazole also has potential implications for the contraindications relating to hypersensitivity. Use is contraindicated in all patients with any type of hypersensitivity to any triazole or imidazole drug.

3.3.4. Clinical efficacy

3.3.4.1. Dose-response study

CL-006

The study evaluated the efficacy of four dose regimens of oteseconazole for the prevention of AVVC through Week 48 in healthy non-pregnant adult females aged <65 years with a history of RVVC. The selection criteria were as used later in Phase 3 (see below). All subjects received treatment for the presenting episode of AVVC with 3 doses of 150 mg fluconazole given 72 h apart. On day 14 from the first dose of fluconazole, subjects who had a clinical signs and symptoms score <3 were randomised into the double-blind Maintenance Phase in which 5 groups of subjects received:

- 150 mg QD for 7 days followed by weekly dosing with 150 mg for 12 or 24 weeks; or
- 300 mg QD for 7 days followed by weekly dosing with 300 mg for 12 or 24 weeks; or
- Matching placebo daily and then weekly.

Dosing was to be within 30 minutes of a meal. All subjects were followed up for a total of 48 weeks.

The primary efficacy measure was the proportion of ITT (all randomised) subjects with one or more episodes of culture-verified AVVC in the Maintenance Phase through Week 48, defined as a positive fungal culture for *Candida* species associated with a clinical signs and symptoms score ≥3. The mITT population included 106 subjects with negative KOH and *Candida* culture as well as a zero-symptom score at baseline (i.e. at the time of randomisation). The mITT2 population (124) had a screening positive culture for Candida and a score of ≥3 and the mITT3 population (59) was the subset that had negative mycology and *Candida* culture with zero symptom score at baseline.

Of the 215 randomised subjects (ITT), 176 (81.9%) completed the study. The mean age was 34.6 years and the mean number of AVVC episodes in the past 12 months was 4.8. Rates for at least one recurrence (protocol-defined AVVC) during the Maintenance Phase in the ITT population were statistically significantly lower in the oteseconazole groups vs. the placebo group.

Similar results were obtained in the mITT, mITT2, mITT3 and PP populations. In the mITT population (those with negative KOH and *Candida* culture and zero symptom score at randomisation), one subject assigned to any oteseconazole dose had a recurrence compared to 13/25 in the placebo group.

Table 11-3 Percentage of Subjects with One or More Culture-Verified Acute VVC Infections through Week 48 (Intent-to-Treat Population)

		VT-1161				
Culture-Verified Acute VVC Infection		150 mg 12 Weeks (N=42)	150 mg 24 Weeks (N=43)	300 mg 12 Weeks (N=43)	300 mg 24 Weeks (N=41)	Placebo (N=46)
Yes	n (%)	2 (4.8%)	3 (7.0%)	0	2 (4.9%)	24 (52.2%)
	95% CI	(0.6%, 16.2%)	(1.5%, 19.1%)	(0.0%, 8.2%)	(0.6%, 16.5%)	(36.9%, 67.1%)
	Odds Ratio [a]	0.0308	0.0414	0.0000	0.0438	
	95% CI [a]	(0.0056, 0.1695)	(0.0088, 0.1944)	(N/A, N/A)	(0.0087, 0.2210)	
	P-value [a]	<0.0001	<0.0001	<0.0001	<0.0001	

Abbreviations: N/A, not applicable; VVC, vulvovaginal candidiasis.

Note: Culture-verified acute VVC infection was defined as a positive fungal culture for *Candida* species associated with clinical signs and symptoms score ≥3. Percentage calculations assumed that subjects who discontinued the study prior to a culture-verified VVC episode (censored subjects) had no episodes. The 95% CIs for the proportion of subjects with 1 or more culture-verified acute VVC infections through Week 48 were calculated using an exact method (Clopper-Pearson).

[a] Odds ratio, corresponding 95% CIs and p-values were from Cochran-Mantel-Haenszel tests comparing each VT-1161 treatment group to placebo stratified by site.

In the mITT3 population (screening positive culture for Candida and a score of ≥3 with negative KOH and *Candida* culture with zero symptom score at baseline), there were no recurrences in any oteseconazole group compared to 11/17 in the placebo group.

In the missing=failure analysis in the ITT population, recurrence rates were 19-35% for oteseconazole groups vs. 63% for placebo.

Table 11-4 Percentage of Subjects with One or More Culture-Verified Acute VVC Infections through Week 48 - Sensitivity Analysis Results (Intent-to-Treat Population)

		VT-1161				
Sensitivity Analysis Method		150 mg 12 Weeks (N=42)	150 mg 24 Weeks (N=43)	300 mg 12 Weeks (N=43)	300 mg 24 Weeks (N=41)	Placebo (N=46)
Kaplan-Meier estimates of proportion at 48 weeks with discontinuations censored at last visit [a]	n %	2 (5.3%)	3 (7.9%)	0	2 (5.3%)	24 (55.8%)
	95% CI	(1.4, 19.8)	(2.6, 22.6)	(N/A, N/A)	(1.4, 19.7)	(41.8, 70.8)
Kaplan-Meier estimates of proportion at 48 weeks with subjects censored at time of missing data [b]	n %	2 (5.3%)	3 (7.9%)	0	1 (2.6%)	24 (57.6%)
	95% CI	(1.3, 19.7)	(2.6, 22.9)	(N/A, N/A)	(0.4, 16.8)	(43.1, 72.9)
Subjects with missing data considered as failures [c]	n (%)	8 (19.0%)	15 (34.9%)	10 (23.3%)	8 (19.5%)	29 (63.0%)
	95% CI	(8.6, 34.1)	(21.0, 50.9)	(11.8, 38.6)	(8.8, 34.9)	(47.5, 76.8)

Abbreviation: VVC, vulvovaginal candidiasis.

Note: Culture-verified acute VVC infection was defined as a positive fungal culture for *Candida* species associated with clinical signs and symptoms score ≥3. The 95% CI was estimated by Kaplan-Meier method unless otherwise specified.

[a] Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified VVC episode were censored at the last nominal visit for which they had signs and symptoms and mycology data.

[b] Subjects with missing signs and symptoms or culture results at a nominal visit that was not preceded by at least 1 culture-verified VVC episode were considered to be censored at the visit with the missing data.

[c] Subjects who were censored in [a] and [b] were considered as failures, i.e., having an episode. The 95% CIs were calculated using an exact method (Clopper-Pearson).

The number of subjects who experienced culture-verified acute VVC episodes (1, 2 or ≥3) through Week 48 was lower in the oteseconazole groups and none who received oteseconazole had 3 or more culture-verified acute VVC episodes through Week 48.

The proportions without clinical signs and symptoms at Weeks 4, 24 and 48 were higher in the 300 mg groups vs. the 150 mg groups and placebo.

The majority of culture-verified AVVC episodes occurred in the first 24 weeks and the figure shows that almost all episodes occurred within the first 12 weeks. There was only one oteseconazole subject (in the 150 mg 12-week group) and 3 placebo group subjects with culture-verified AVVC between weeks 24 and 48. Almost all the culture-verified AVVC episodes were due to *C. albicans*.

3.3.4.2. Main studies

Study participants
Eligible female subjects were to have a history of RVVC defined by ≥3 patient-reported episodes of AVVC in the past 12 months, including the presenting episode at screening. At least one pre-screening episode was to have been documented by a positive culture or US-approved diagnostic test. At screening, they were to have an AVVC episode defined as:
a. Total signs and symptoms score of ≥3 and
b. Positive KOH wet mount preparation or Gram stain from a vaginal smear revealing filamentous hyphae/pseudohyphae and/or budding yeast cells.

The composite signs and symptoms score of ≥3 was derived from a scale of 0 to 3 (absent, slight, moderate, severe) applied to:
(a) Signs: erythema, oedema and excoriation;
(b) Symptoms: itching, burning, and irritation.

Treatments
Subjects were instructed to take all doses with water within 30 minutes after ingestion of their main meal of the day and at approximately the same time of the day throughout the study.

CL-011 and -012

- In the *Induction Phase*, all subjects received 3 doses of 150 mg fluconazole (locally sourced) administered 72 hours apart. Subjects with a score <3 at ~day 14 after start of fluconazole were randomised into the studies.
- In the *Maintenance Phase* (post-randomisation through Week 48), subjects received oteseconazole 150 mg QD on days 1-7 and 150 mg once weekly for 11 doses starting on day 14 or matching placebo. In case of an episode of AVVC (i.e. a recurrence), the investigator could prescribe fluconazole 150 mg or other treatment if fluconazole was ineffective.

CL-017
Eligible subjects with a qualifying episode of AVVC were randomised to one of:

- Oteseconazole 600 mg on Day 1 and 450 mg on Day 2
- Fluconazole 3 doses of 150 mg every 72 hours

Days 1-14 constituted the *Induction Phase*. On ~Day 14, subjects with a clinical signs and symptoms score <3 entered the 48-week *Maintenance Phase* (weeks 2-50 from randomisation). On day ~14, subjects initially randomised to oteseconazole commenced 150 mg QW and those initially randomised to fluconazole commenced placebo QW, each for 11 weeks.

Objectives

CL-011 and -012

The primary objective was to evaluate efficacy for RVVC through Week 48.

CL-017

The primary objectives were:

- To evaluate efficacy in the prevention of culture-verified AVVC through Week 50 in RVVC subjects
- To compare the efficacy of oteseconazole and fluconazole for treatment of AVVC in RVVC subjects

Outcomes/endpoints

CL-011 and -012

The primary efficacy endpoint was a culture-verified AVVC episode (positive culture for *Candida* species and a clinical signs and symptoms score ≥3) during the Maintenance Phase (from randomisation to week 48), with proportions of subjects with an event calculated for the ITT population. Case ascertainment occurred at post-randomisation visits at weeks 2, 6, 12 (end of treatment), 18, 24, 30, 36, 42 and 48. Unscheduled visits occurred if AVVC was suspected by the subject.

The most important secondary endpoints were:

- Time to first recurrence of a culture-verified AVVC episode with signs and symptoms score ≥3 during the Maintenance Phase
- The proportion with at least 1 positive culture for *Candida* during the Maintenance Phase
- The proportion with at least 1 culture-verified AVVC episode with signs and symptoms score ≥3 post-randomisation through Week 24

CL-017

The primary efficacy measure was the proportion of subjects with 1 or more culture-verified AVVC episodes (defined as in CL-011 and -012 but counting from randomisation through Week 50) in the ITT population, which included subjects who failed to clear their infection during the Induction Phase. Case ascertainment occurred at scheduled visits at weeks 2 (test of cure for acute treatment), 8, 14 (end of treatment), 20, 26, 32, 38, 44 and 50. Unscheduled visits occurred if acute VVC was suspected.

The secondary endpoints were:

- The proportion of subjects with resolved AVVC (clinical signs and symptoms score of <3) at Day 14 following start of treatment with oteseconazole or fluconazole
- The proportion of subjects with at least 1 culture-verified AVVC episode with signs and symptoms score of ≥3 during the Maintenance Phase counting from Day 14 through Week 50
- Time to first recurrence of a culture-verified AVVC with signs and symptoms score ≥3 during the Maintenance Phase (post-Day 14 through Week 50)
- The proportion of subjects with at least 1 positive culture for *Candida* during the Maintenance Phase (post-Day 14 through Week 50).

Sample size

CL-011 and 012

A sample size of 68 active and 34 placebo subjects was to provide at least 95% power to detect a treatment difference of 35% for the percentages meeting the primary endpoint. However, to address the secondary endpoint based on change in the SF-36 MCS with an SD of 10 points (2-sample t-test, alpha=0.05) and adjusting for the expected discontinuation rate, ~300 subjects were required.

CL-017

The study planned to enrol 180 subjects (120 oteseconazole and 60 fluconazole/placebo). A sample size of 82 oteseconazole and 41 fluconazole/placebo subjects would provide at least 90% power to detect a treatment difference in the percentage with 1 or more culture-verified AVVC episodes during the Maintenance Phase (Fisher's exact test, 2-sided alpha=0.05, assuming 50% recurrence in the control group). The sample size was powered to detect at least a 35% separation between the treatment groups.

For the secondary endpoint of resolved AVVC at Day 14 (clinical signs and symptoms score of <3), 120 oteseconazole and 60 fluconazole/placebo subjects would provide at least 88% power to detect non-inferiority with a margin of 15% (see below). This assumes a (2-sided) type 1 error rate of 0.05 (Z-test for 2 independent proportions, 1-sided alpha=0.025) and a fluconazole resolution rate of 90%.

Randomisation

An IWRS was used to randomise subjects in a 2:1 ratio to oteseconazole or placebo in all three studies.

Blinding (masking)

CL-011 and -012 were double blind and placebo-controlled.
CL-017 was double blind and active (fluconazole) controlled with a double dummy design in the Induction Phase (days 1-14). A double-blind and placebo-controlled design applied from weeks 2-14.

Statistical methods

Analysis populations

- ITT = all randomised; primary analysis population for evaluation of prevention of recurrence
- Modified Intent-to-Treat (mITT) = all randomised with a positive central laboratory KOH at screening, a positive culture at screening and a negative culture at the time of randomisation in CL-011 and -012 or at Day 14 post-randomisation in CL-017
- Per-Protocol (PP) = all randomised with no deviations to inclusion/exclusion criteria that could affect treatment outcome, who were adherent to treatment (≥80% in week 1 and then ≥50%), had a Week 48 (CL-011 and -012) or 50 (CL-017) visit (±14 days) and no major protocol violations that would impact treatment outcome

In CL-017, the following additional analysis populations were defined:

- Induction Phase mITT Population = all randomised with a positive central KOH test at screening and a positive culture at screening
- Induction Phase PP Population= all randomised with no deviations to inclusion/exclusion criteria that could affect treatment outcome during the Induction Phase, with ≥80% adherence and no major protocol violations; primary analysis population for evaluation of treatment of AVVC

Primary analysis

The primary efficacy endpoint was analysed using a Chi-square test for active treatment vs. placebo based on the ITT population. The proportions of subjects with such an episode were to be compared. AVVC with a positive culture for any species of Candida were included in the primary endpoint. Subjects who received VVC medication without meeting the definition of a culture-verified AVVC were not treated as experiencing a recurrent episode in the primary analysis of the primary endpoint.

Secondary analyses

Hierarchical testing of secondary endpoints in CL-017 followed the same order as the listed secondary endpoints.

Non-inferiority for the proportion of subjects with resolved AVVC at Day 14 following start of treatment with oteseconazole vs. fluconazole was evaluated in the Induction Phase PP Population. If the lower limit of the 95% CI for the difference in proportions between the oteseconazole arm and the fluconazole arm was greater than -15%, then NI was claimed.

Missing Data

Section 3.4.4 in each of the SAPs covers *Missing data and outliers.*

- For scheduled visits where the investigator's assessment of clinical signs and symptoms or the culture result was missing, missing values were to be imputed using multiple imputation (MI).
- For subjects who discontinued the study early and had missing assessments for all visits after discontinuation, the missing values were to be imputed using MI.

The missing values were to be imputed using the following auxiliary information: region, treatment, BMI, age, ethnicity and visit.

The procedure PROC MI in SAS was to be used to generate 10 possible imputed datasets. Using these multiple imputation datasets, determination of meeting the primary endpoint of a culture-verified acute VVC episode during the Maintenance Phase was to be derived. Subjects with a culture-verified acute VVC episode at any point from post Day 14 through Week 50 (including unscheduled visits) and subjects with an unresolved VVC episode during the Induction Phase (post-randomisation through Day 14) were to be counted as having an episode when calculating the primary endpoint. The multiple datasets containing the primary endpoint were to be analysed using a Chi-square test and the results were to be combined using PROC MIANALYZE to obtain an inferential result. Sensitivity analyses were planned for the primary endpoint to assess the impact of missing/censored data on the results:

1. The first sensitivity analysis used Kaplan-Meier methods to estimate the proportion of subjects with one or more culture-verified acute VVC episodes post randomisation through Week 50. The Kaplan-Meier estimate and 95% confidence interval was determined and compared to the primary result. For this analysis, time to event and censoring was calculated using the following rules:
a. Subjects who experienced a culture-verified acute VVC episode post randomisation through Week 50 had their time to event calculated as the time in weeks from randomisation to the first culture-verified acute VVC episode.
b. Subjects who discontinued the study for any reason prior to Week 50 without experiencing a culture-verified acute VVC episode were censored at the last nominal visit for which they had signs and symptoms and culture data.
c. Subjects who had missing data at any point prior to Week 50, who did not experience a culture-verified acute VVC episode and had both non-missing signs and symptoms data at Week 50 and non-missing culture data at Week 50 were censored at the Week 50 visit.

2. The second sensitivity analysis was conducted as for the first but time to event and censoring was calculated using the following rules:
a. Subjects who experienced a culture-verified acute VVC episode post randomisation through Week 50 had time to event calculated in weeks from randomisation to first culture-verified acute VVC episode.
b. Subjects who discontinued the study for any reason prior to Week 50 and had no nominal visits with missing signs and symptoms or culture data prior to discontinuation were censored at the last nominal visit prior to discontinuation for which they had signs and symptoms and culture data.
c. Subjects with no culture-verified acute VVC episode post randomisation through Week 50 with missing signs and symptoms or culture data at any point not due to COVID-19 were censored at the last nominal visit before the first visit with missing signs and symptoms and culture data not due to COVID-19. Subjects who reached Week 50 without a culture-verified acute VVC episode and without any missing data, not due to COVID-19, were censored at Week 50. Subjects who did not experience a

culture-verified acute VVC episode post randomisation through Week 50 with the only missing signs and symptoms or culture data due to COVID-19 were censored at the last nominal visit for which they had signs and symptoms and culture data.
3. Subjects censored for the second sensitivity analysis due to early discontinuation or missing data not due to COVID-19 were counted as failures, i.e. as having had an episode. The denominator for the calculation was the ITT population.

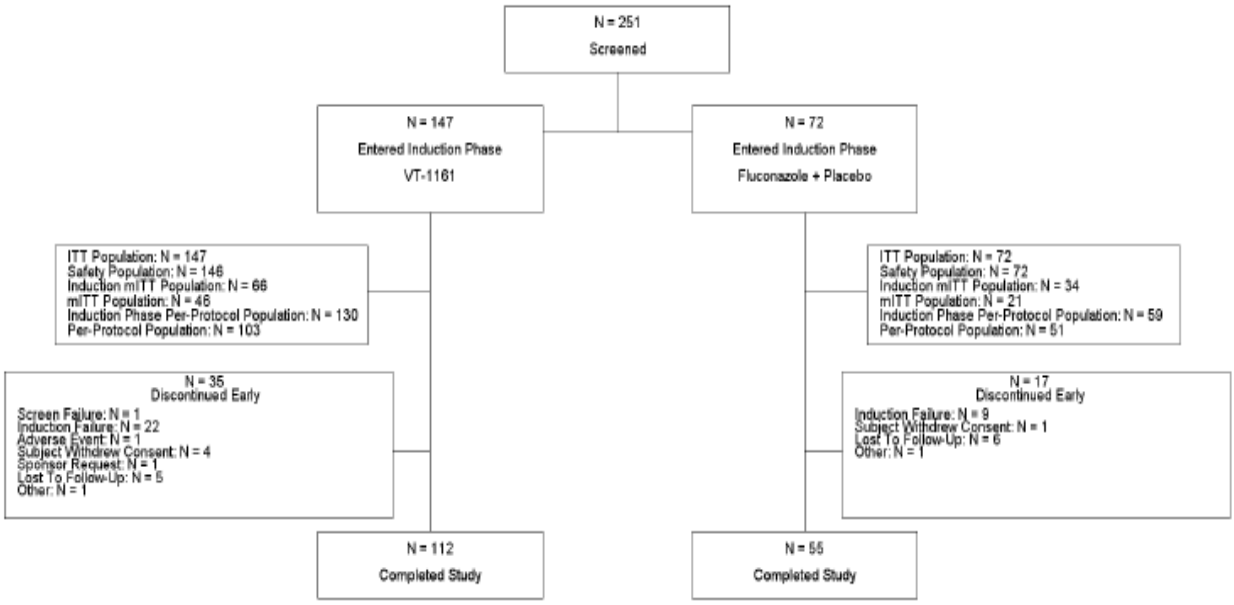
4. A completer analysis was performed where subjects who did not have a culture-verified acute VVC episode and had missing assessments for a given visit or discontinued from the study prior to Week 50 were excluded from the analysis.

5. The primary analysis method was used to analyse a modified definition of the primary endpoint where subjects were included as having an acute VVC episode if 1) they met the primary endpoint definition or 2) they had a recurrence in the absence of Investigator confirmed signs and symptoms and/or culture confirmation but took a medication known to treat VVC during the Maintenance Phase.

In CL017, for the secondary analysis of the proportion with resolved acute VVC infections (clinical signs and symptoms score of < 3) at Day 14 following treatment with oteseconazole or fluconazole, missing values were imputed along the same lines as described above for the primary analysis. For the first sensitivity analysis, any subjects with missing Day 14 assessments were counted as not having resolved the presenting AVVC episode. For the second sensitivity analysis, subjects who did not complete the Day 14 assessment were excluded from the analysis.

Results CL-017

Subject disposition is summarised in the figure.



There were 425 protocol deviations reported in 160 subjects. Most of the major protocol deviations were related to eligibility and entry criteria (13 and 7). The mean (SD) age of subjects was 35 (11.0) years. There was no notable difference observed in demographics and baseline characteristics between the treatment groups. All subjects had experienced at least 3 acute VVC infections in the past 12 months, with the majority reporting 3 to 4 episodes (range: 3 to 20).

At the Screening Visit (Day 1), 40% had cultures positive for *C. albicans* and 2% had cultures positive for *C. glabrata*. Numbers analysed by defined population are shown below.

Table 5: Subject Screening, Enrollment, and Disposition (All Subjects)

	Oteseconazole (N=147) n (%)	Fluconazole/Placebo (N=72) n (%)	Overall (N=251) n (%)
Subjects screened			251
Subjects randomized (i.e., subjects who entered the Induction Phase)	147	72	219
Subjects treated	146 (>99%)	72 (100%)	218 (>99%)
Subjects who entered the Maintenance Phase	123	62	185
Subjects in the ITT Population [a]	147 (100%)	72 (100%)	219 (100%)
Subjects in the Safety Population [b]	146 (>99%)	72 (100%)	218 (>99%)
Subjects in the Induction mITT Population [c]	66 (45%)	34 (47%)	100 (46%)
Subjects in the mITT Population [d]	46 (31%)	21 (29%)	67 (31%)
Subjects in the Induction Phase PP Population [e]	130 (88%)	59 (82%)	189 (86%)
Subjects in the PP Population [f]	103 (70%)	51 (71%)	154 (70%)
Subjects completed	112 (76%)	55 (76%)	167 (76%)

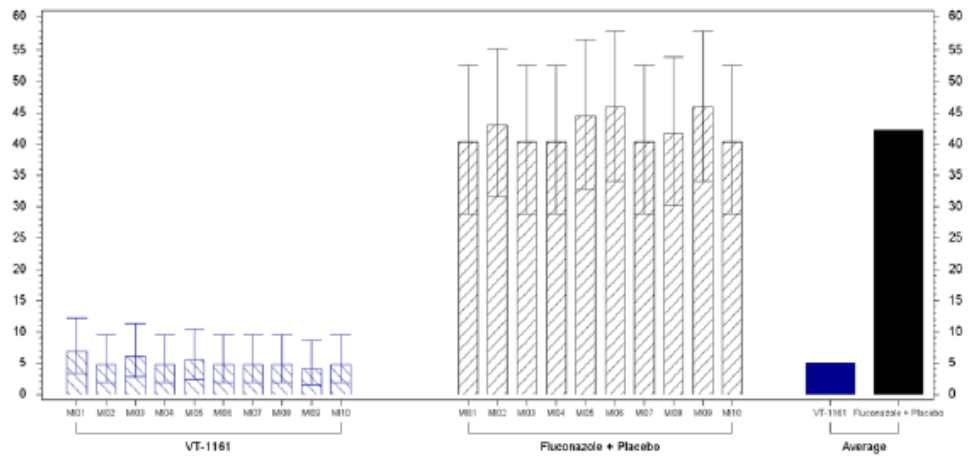
The average percentage (derived by applying MI; see above) of subjects with ≥1 culture-verified AVVC episode through Week 50 was lower in the oteseconazole group (5.1% vs. 42.2%).

Table 11: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode Post-randomization Through Week 50 (ITT Population)

≥1 Culture-verified acute VVC episodes (Missing value imputed with MI) [a]	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)
Average percentage	5.1%	42.2%
Minimum, maximum percentage	4.1%, 6.8%	40.3%, 45.8%
P-value [b]	<0.001	

Abbreviations: ITT=intent-to-treat; MI=multiple imputation; VVC=vulvovaginal candidiasis
a Missing values were imputed with MI using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit.
b The p-value was obtained using a Chi-square test comparing oteseconazole with fluconazole/placebo.

Figure 2: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode by Treatment Group (ITT Population)



The observed rate of culture-verified AVVC at week 50 was 4/120 (3%) in the oteseconazole group and 24/60 (40%) in the fluconazole/placebo group, with denominators based on numbers with data at the visit. Using the ITT population denominators, the rates would be 2.7% vs. 33% and 24/28 documented episodes were due to *C. albicans*.

Table 27: Acute VVC Recurrence by Week 50 by Pathogen (ITT Population)

Acute VVC Recurrence by Week 50	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)
Recurrence	4 (3%)	24 (40%)
No Recurrence	116 (97%)	36 (60%)
P-value [a]	<0.001	
Recurrence by Week 50, n (%) [95% CI]		
Candida albicans	3 (3%) [1%, 7%]	21 (35%) [23%, 48%]
Candida glabrata	0 (0%) [0%, 3%]	3 (5%) [1%, 14%]
Candida parapsilosis	1 (<1%) [0%, 5%]	0 (0%) [0%, 6%]

Abbreviations: CI=confidence interval; ITT=intent-to-treat; VVC=vulvovaginal candidiasis
Note: The value at each visit was the number of subjects who had a culture-verified acute VVC episode by that visit.
[a] The P-value was obtained from a Fisher's exact test comparing oteseconazole to fluconazole/placebo.

By each sensitivity analysis method, the average percentage of subjects with ≥1 culture-verified acute VVC episode (post-randomisation through Week 50) was lower in the oteseconazole group compared to the fluconazole/placebo group in the ITT Population. The between-group differences were statistically significant when subjects with missing data were counted as failures (M=F), for subjects without any missed visits, and when subjects who took medication known to treat VVC were counted as failures.

Table 12: Sensitivity Analyses: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode (ITT Population)

≥1 Culture-verified Acute VVC Episode Sensitivity Analysis Method	Oteseconazole (N=147)	Fluconazole/Placebo (N=72)
Kaplan-Meier estimates of proportion with discontinuations censored at last visit [a]		
n (censored)	142 (136)	68 (42)
Percent	4.9%	43.3%
95% CI	2.2%, 10.5%	31.8%, 56.8%
Kaplan-Meier estimates of proportion with subjects censored at time of missing data [b]		
n (censored)	142 (136)	68 (42)
Percent	4.9%	43.7%
95% CI	2.2%, 10.6%	32.1%, 57.3%
Subjects with missing data counted as failures [c]		
n (%)	44 (29.9%)	40 (55.6%)
95% CI	22.7%, 38.0%	43.4%, 67.3%
P-value	<0.001	
Subjects without any missing visits [d]		
n/number included in analysis (%)	6/109 (5.5%)	26/58 (44.8%)
95% CI	2.0%, 11.6%	31.7%, 58.5%
P-value	<0.001	

The rates for positive cultures regardless of clinical scores by visit in the ITT population were higher than rates for the primary endpoint, such that by week 50 the cumulative percentages were 22/120 (18%) for oteseconazole and 43/60 (72%) for placebo using denominators based on the numbers that attended the visit.

Based on the applicant's pre-defined NI margin, oteseconazole was non-inferior to fluconazole for the average percentage with resolved AVVC (clinical signs and symptoms score <3) in the Induction Phase PP Population at Day 14 (93.1% oteseconazole vs. 98.3% fluconazole; Wald 95% CI=-10.7%, 0.2% for difference in proportions). For comparisons in the ITT and mITT populations, the lower bounds of the Wald 95% CI were within -10%.

Table 15: Proportion of Subjects with Resolved Acute VVC Infections at Day 14 (Induction Phase PP, ITT, and Induction Phase mITT Populations)

Subjects with resolved acute VVC infections at Day 14 [a]	Oteseconazole	Fluconazole/Placebo
Induction Phase PP Population	**(N=130)**	**(N=59)**
Average Percentage	93.1%	98.3%
Minimum, Maximum Percentage	93.1%, 93.1%	98.3%, 98.3%
95% CI [b]	-10.7%, 0.2%	
ITT Population	**(N=147)**	**(N=72)**
Average Percentage	93.2%	95.8%
Min, Max Percentage	93.2%, 93.2%	95.8%, 95.8%
95% CI [b]	-8.8%, 3.5%	
Induction Phase mITT Population	**(N=66)**	**(N=34)**
Average Percentage	98.5%	94.1%
Min, Max Percentage	98.5%, 98.5%	94.1%, 94.1%
95% CI [b]	-4.1%, 12.8%	

Abbreviations: CI=confidence interval; ITT=intent-to-treat; MI=multiple imputation; mITT=modified intent-to-treat; PP=per-protocol; VVC=vulvovaginal candidiasis
[a] Missing values were imputed with MI using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit.
[b] The Wald 95% CI was for the difference in proportions.

When subjects with missing Day 14 data were counted as failures or were excluded from the analysis, the lower bounds of the Wald 95% CI exceeded -10%.

Table 16: Sensitivity Analysis: Proportion of Subjects with Resolved Acute VVC Infections at Day 14 (Induction Phase PP Population)

Resolved acute VVC infections at Day 14	Oteseconazole (N=130)	Fluconazole/Placebo (N=59)
Subjects with missing Day 14 [a]		
n (%)	118 (90.8%)	58 (98.3%)
95% CI	84.4%, 95.1%	90.9%, 100.0%
95% CI [b]	-14.3%, 0.9%	
Subjects without missing Day 14 [c]		
n/Number included in analysis (%)	118/127 (92.9%)	58/59 (98.3%)
95% CI	87.0%, 96.7%	90.9%, 100.0%
95% CI [b]	-11.8%, 2.9%	

Abbreviations: CI=confidence interval; MI=multiple imputation; PP=per-protocol; VVC=vulvovaginal candidiasis
[a] Subjects with missing Day 14 were counted as not having resolved their acute VVC infection. The 95% CI was calculated using an exact method (Clopper-Pearson).
[b] The 95% CI for difference was calculated using an exact method (Clopper-Pearson).
[c] Only subjects with Day 14 signs and symptoms data were included in the analysis. The 95% CI was calculated using an exact method (Clopper-Pearson).

Based on the applicant's NI margin, oteseconazole was non-inferior to fluconazole for the average percentage with resolved AVVC at Day 14 by age (18-33 and 34+ years) and in those with 4+ prior episodes of RVVC.

In the Induction Phase PP Population, the average percentage of subjects with a clinical signs and symptoms score of 0 at Day 14 was comparable in the oteseconazole and fluconazole groups.

Table 28: Proportion of Subjects with Clinical Signs and Symptoms Score of 0 at Day 14 (Induction Phase PP, Induction Phase mITT, and ITT Populations)

Clinical Signs and Symptoms Score of 0 (Missing value imputed with MI [a])	Oteseconazole	Fluconazole/Placebo
Induction Phase PP Population, N	**130**	**59**
Average Percentage	41.8%	39.0%
Minimum, Maximum Percentage	41.5%, 43.1%	39.0%, 39.0%
95% CI [b]	-12.2%, 18.0%	
Induction Phase mITT Population, N	**66**	**34**
Average Percentage	49.7%	35.9%
Minimum, Maximum Percentage	48.5%, 51.5%	35.3%, 38.2%
95% CI [b]	-6.6%, 34.2%	
ITT Population, N	**147**	**72**
Average Percentage	43.5%	35.1%
Minimum, Maximum Percentage	42.9%, 44.9%	34.7%, 36.1%
95% CI [b]	-5.4%, 22.2%	

Abbreviations: CI=confidence interval; ITT=intent-to-treat; MI=multiple imputation; mITT=modified intent-to-treat; PP=per-protocol

[a] Missing values were imputed with MI using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit.

[b] Wald 95% CI for the difference in proportions between oteseconazole and fluconazole.

The average percentages with clinical signs and symptoms of 0 plus negative cultures for *Candida* species at Day 14 were comparable or slightly higher for oteseconazole.

Table 29: Proportion of Subjects with Clinical Signs and Symptoms Score of 0 and Negative Culture for *Candida* Species at Day 14 (Induction Phase PP, Induction Phase mITT, and ITT Populations)

Clinical Signs and Symptoms Score of 0 and Negative Culture for *Candida* Species (Missing value imputed with MI [a])	Oteseconazole	Fluconazole/Placebo
Induction Phase PP Population, N	**130**	**59**
Average Percentage	35.7%	35.6%
Minimum, Maximum Percentage	35.4%, 36.9%	35.6%, 35.6%
95% CI [b]	-14.7%, 14.9%	
Induction Phase mITT Population, N	**66**	**34**
Average Percentage	35.9%	29.7%
Minimum, Maximum Percentage	34.8%, 37.9%	29.4%, 32.4%
95% CI [b]	-13.2%, 25.6%	
ITT Population, N	**147**	**72**
Average Percentage	37.3%	32.2%
Minimum, Maximum Percentage	36.7%, 38.1%	31.9%, 33.3%
95% CI [b]	-8.3%, 18.5%	

Abbreviations: CI=confidence interval; ITT=intent-to-treat; MI=multiple imputation; mITT=modified intent-to-treat; PP=per-protocol

[a] Missing values were imputed with MI using the following auxiliary information: treatment, baseline body mass index, baseline age, ethnicity, and visit.

[b] Wald 95% CI for the difference in proportions between oteseconazole and fluconazole.

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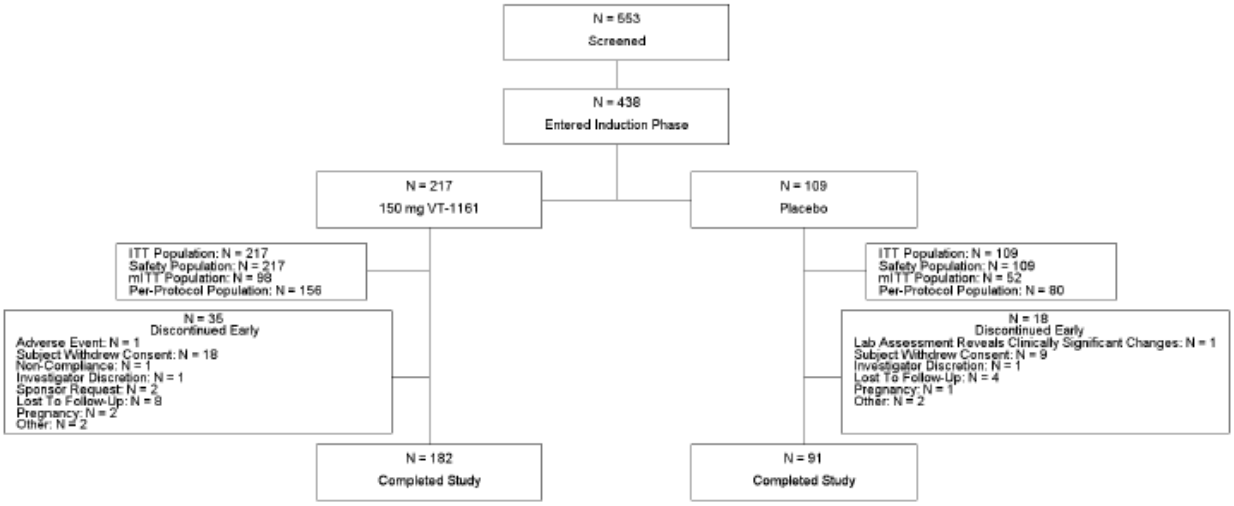
Subject disposition is shown in the figure.



There were 1036 protocol deviations reported in 288 subjects. Most common were those related to visit schedule (oteseconazole 84 subjects, placebo 57 subjects), study procedures (86 and 53), eligibility and entry (70 and 33) and laboratory assessments (63 and 36).

The mean (SD) age of subjects was 34 (10.2) years. There was no notable difference observed in demographics and baseline characteristics across the treatment groups. All subjects had experienced at least 3 AVVC episodes in the past 12 months, with the majority reporting 3 to 4 episodes (range: 3 to 20). At screening, 51% had cultures positive for *C. albicans* and 6% had cultures positive for *C. glabrata*. At baseline (time of randomisation), 8% of subjects had cultures positive for *C. albicans* and 5% had cultures positive for *C. glabrata*.

Numbers in defined analysis populations are shown below.

Table 4: Subject Screening, Enrollment, and Disposition (All Subjects)

	Oteseconazole (N=217) n (%)	Placebo (N=109) n (%)	Overall (N=553) n (%)
Subjects screened			553
Subjects in Induction Phase			438
Subjects randomized	217	109	326
Subjects treated	217 (100%)	109 (100%)	326 (100%)
Subjects in the ITT Population [a]	217 (100%)	109 (100%)	326 (100%)
Safety Population [b]	217 (100%)	109 (100%)	326 (100%)
Subjects in the mITT Population [c]	98 (45%)	52 (48%)	150 (46%)
Per-Protocol Population [d]	156 (72%)	80 (73%)	236 (72%)
Subjects Completed Study	182 (84%)	91 (83%)	273 (84%)

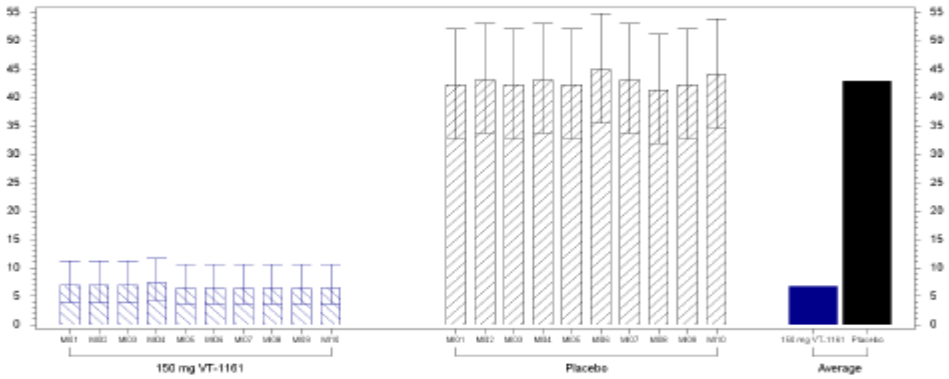
The average percentage of subjects with ≥1 culture-verified AVVC episode through Week 48 was lower in the oteseconazole group (6.7%) compared with the placebo group (42.8%). The results observed in the mITT and PP Populations were similar to those in the ITT Population.

Table 10: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode during the Maintenance Phase (ITT Population)

≥1 Culture-verified Acute VVC Episode (Missing value imputed with MI) [a]	Oteseconazole (N=217)	Placebo (N=109)
Average Percentage	6.7%	42.8%
Minimum, Maximum Percentage	6.5%, 7.4%	41.3%, 45.0%
P-value [b]	<0.001	

Abbreviations: ITT=intent-to-treat; MI=multiple imputation; VVC=vulvovaginal candidiasis
a. Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.
b. The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Figure 2: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode during the Maintenance Phase by Treatment Group (ITT Population)



Abbreviations: ITT=intent-to-treat; MI=multiple imputation (numbers denote MI groups); SAP=Statistical Analysis Plan; VT-1161=oteseconazole; VVC=vulvovaginal candidiasis
Note: Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

Cumulative culture-verified AVVC rates in the ITT population at Week 48 were 7% (14/212) for oteseconazole vs. 42% (45/106) for placebo using denominators of number attending visit.

Table 27: Acute VVC Recurrence by Week 48 by Pathogen (ITT Population)

Acute VVC Recurrence at Week 48	Oteseconazole (N=217)	Placebo (N=109)
Recurrence	14 (7%)	45 (42%)
No Recurrence	198 (93%)	61 (58%)
P-value [a]	<0.001	
Recurrence n (%) [95% CI]		
Candida albicans	7 (3%) [1%, 7%]	41 (39%) [29%, 49%]
Candida dubliniensis	0 (--) [0%, 2%]	1 (<1%) [0%, 5%]
Candida glabrata	5 (2%) [1%, 5%]	3 (3%) [1%, 8%]
Candida nivariensis	1 (<1%) [0%, 3%]	0 (--) [0%, 3%]
Candida parapsilosis	1 (<1%) [0%, 3%]	0 (--) [0%, 3%]

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward, LS=least squares
a. The p-value was obtained from a Fisher's exact test comparing active treatment to placebo.

The between-group differences for the primary endpoint were statistically significant when subjects with missing data were counted as failures, for subjects without any missed visits and when subjects who took medication known to treat VVC were counted as failures.

Table 11: Sensitivity Analyses: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode during the Maintenance Phase (ITT Population)

≥1 Culture-verified Acute VVC Episode Sensitivity Analysis Method	Oteseconazole (N=217)	Placebo (N=109)
Kaplan-Meier estimates of proportion with discontinuations censored at last visit [a]		
n (censored)	212 (198)	106 (61)
Percent	7.6%	43.7%
95% CI	4.5%, 12.6%	34.7%, 53.8%
Kaplan-Meier estimates of proportion with subjects censored at time of missing data [b]		
n (censored)	210 (196)	106 (61)
Percent	7.8%	44.0%
95% CI	4.7%, 13.0%	34.9%, 54.2%
Subjects with missing data counted as failures [c]		
n (%)	56 (25.8%)	56 (51.4%)
95% CI	20.1%, 32.2%	41.6%, 61.1%
P-value	<0.001	
Subjects without any missing visits [d]		
n/number included in analysis (%)	14/175 (8.0%)	45/98 (45.9%)
95% CI	4.4%, 13.1%	35.8%, 56.3%
P-value	<0.001	
Subjects who took medication known to treat VVC counted as failures, missing values imputed using MI [e]		
Average Percentage	27.3%	50.8%
Min, Max Percentage	27.2%, 27.6%	49.5%, 52.3%
P-value	<0.001	

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease of 2019; ITT=intent-to-treat; MI=multiple imputation; VVC=vulvovaginal candidiasis

a. Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified acute VVC episode were censored at the last nominal visit for which they had signs and symptoms and culture data. Subjects who had missing data at any point prior to Week 48 and had both nonmissing signs and symptoms and culture data at Week 48 were censored at Week 48.

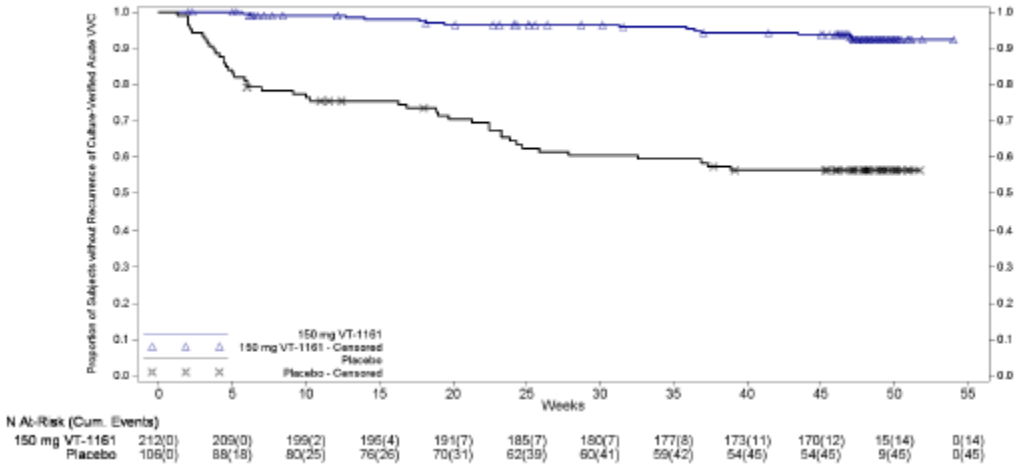
b. Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified acute VVC episode were censored at the last nominal visit for which they had signs and symptoms and culture data. Subjects who had missing data at any point prior to Week 48 that was not due to COVID-19 were censored at the last nominal visit before the first visit with missing signs and symptoms and culture data not due to COVID-19. Subjects who reached Week 48 without a culture-verified acute VVC episode and without any missing data were censored at Week 48.

c. Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified acute VVC episode were counted as having an episode at the time of discontinuation. Subjects who had missing data at any point prior to Week 48 not due to COVID-19 were counted as having an episode at the last nominal visit before the first visit with missing signs and symptoms and culture data. Subjects who reached Week 48 without a culture-verified acute VVC episode and without any missing data not due to COVID-19 were counted as not having a recurrence. The 95% CI was calculated using an exact method (Clopper-Pearson). The p-value was from a Chi-square test.

The first exploratory analysis of the primary endpoint (logistic regression with factors for treatment and screening signs and symptoms score) showed that the screening signs and symptoms score was not a statistically significant factor for predicting whether a subject had a relapse during the 48 weeks following clearance of an acute infection (p=0.777 in the ITT Population). After controlling for the number of historic VVC episodes, oteseconazole was superior to placebo based on the average percentage of ITT subjects with ≥1 culture-verified AVVC episode through Week 48 (p<0.001).

The Kaplan-Meier plot indicates that most recurrences occurred during or shortly after completing the 12-week treatment course.

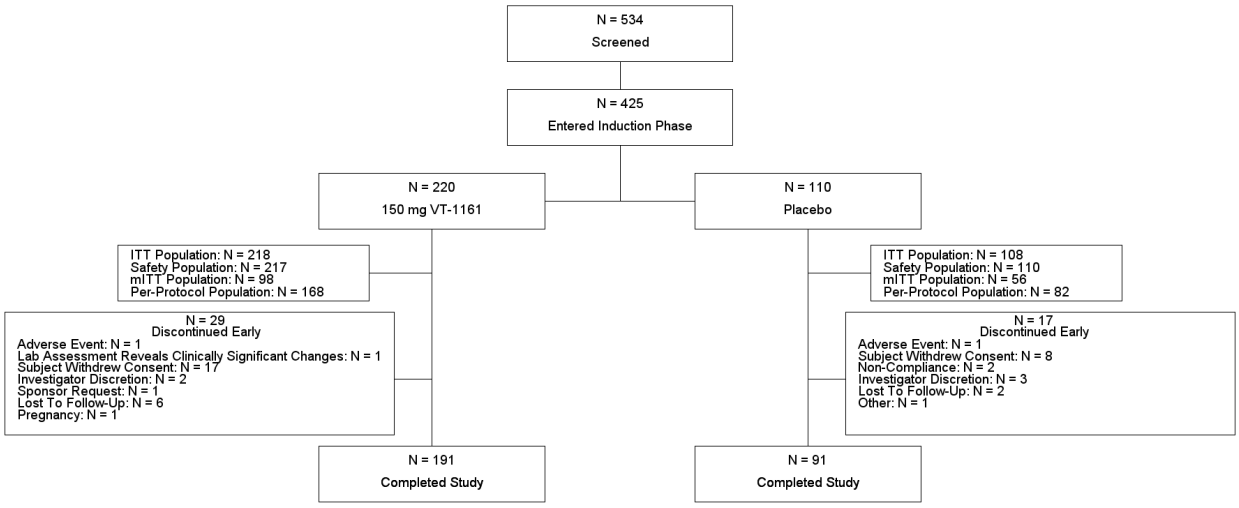
Figure 3: Kaplan-Meier Plot of Time to First Recurrence of Culture-verified Acute VVC Episode (ITT Population)



Oteseconazole was superior to placebo with reference to the average percentage of ITT subjects with ≥1 culture-verified AVVC episode through Week 12 (1.8% vs. 23.9%; p<0.001) and through Week 24 (3.3% vs. 37.4%; p<0.001).

Results CL-012

Subject disposition is shown in the figure.



One study site was closed due to multiple GCP violations. The 4 subjects enrolled at this site were excluded from the ITT population.

There were 1017 protocol deviations reported in 293 subjects. The most common deviations were related study procedures (oteseconazole 92, placebo 50), eligibility and entry (81 and 40), laboratory assessments (80 and 39) and visit schedule (74 and 42 subjects). Rates and types of deviations were very similar between treatment groups.

The mean (SD) age of subjects was 34 (9.9) years. A majority of the subjects were White (289 [89%]) and not of Hispanic or Latino ethnicity (277 [85%]). There was no notable difference observed in demographics and baseline characteristics across the treatment groups.

All subjects had experienced at least 3 acute VVC infections in the past 12 months, with the majority reporting 3 to 4 episodes (range: 3 to 20). At screening, 50% had cultures positive for *C. albicans* only and 5% had cultures positive for *C. glabrata.* At baseline, 6% had cultures positive for *C. albicans* only and 2% for *C. glabrata or C. parapsilosis* only while 4 had cultures positive for more than one species. There was no notable difference in RVVC history or pathogen distribution across treatment groups.

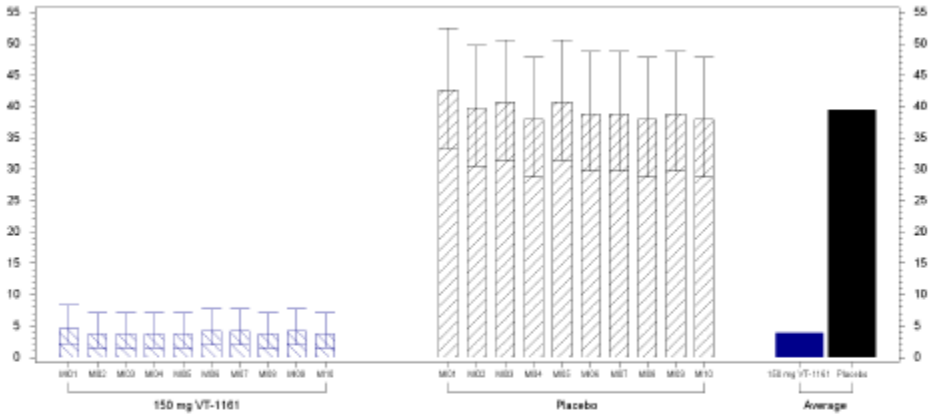
Numbers in predefined analysis populations are shown below.

Table 4: Subject Screening, Enrollment, and Disposition (All Subjects)

	Oteseconazole (N=220) n (%)	Placebo (N=110) n (%)	Overall (N=534) n (%)
Subjects screened			534
Subjects in Induction Phase			425
Subjects randomized	220	110	330
Subjects treated	217 (99%)	110 (100%)	327 (>99%)
Subjects in the ITT Population [a]	218 (>99%)	108 (98%)	326 (99%)
Safety Population [b]	217 (99%)	110 (100%)	327 (>99%)
Subjects in the mITT Population [c]	98 (45%)	56 (51%)	154 (47%)
Per-Protocol Population [d]	168 (76%)	82 (75%)	250 (76%)
Subjects Completed Study	191 (87%)	91 (83%)	282 (85%)

In the ITT population, the average percentage of subjects with ≥1 culture-verified AVVC episode with a signs and symptoms score ≥3 through Week 48 was lower in the oteseconazole treatment group (3.9%) compared with the placebo group (39.4%).

Figure 2: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode during the Maintenance Phase by Treatment Group (ITT Population)



Abbreviations: ITT=intent-to-treat; MI=multiple imputation; SAP=Statistical Analysis Plan; VT 1161=oteseconazole; VVC=vulvovaginal candidiasis
Note: Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.

Table 10: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode during the Maintenance Phase (ITT Population)

≥1 Culture-verified Acute VVC Episode (Missing value imputed with MI) [a]	Oteseconazole (N=218)	Placebo (N=108)
Average Percentage	3.9%	39.4%
Minimum, Maximum Percentage	3.7%, 4.6%	38.0%, 42.6%
P-value [b]	<0.001	

Abbreviations: ITT=intent-to-treat; MI=multiple imputation (numbers denote MI groups); VVC=vulvovaginal candidiasis
a. Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.
b. The p-value was obtained using a Chi-square test comparing active treatment to placebo.

Based on cumulative episodes meeting the primary endpoint definition, by Week 48 the rates were 8/213 (4%) in the oteseconazole group and 39/107 (36%) in the placebo group, using denominators based on numbers attending the visit.

Table 27: Acute VVC Recurrence by Week 48 by Pathogen (ITT Population)

Acute VVC Recurrence at Week 48	Oteseconazole (N=218)	Placebo (N=108)
Recurrence	8 (4%)	39 (36%)
No Recurrence	205 (96%)	68 (64%)
P-value [a]	<0.001	
Recurrence n (%) [95% CI]		
Candida albicans	5 (2%) [1%, 5%]	39 (36%) [27%, 46%]
Candida dubliniensis	2 (<1%) [0%, 3%]	0 (--) [0%, 3%]
Candida glabrata	1 (<1%) [0%, 3%]	0 (--) [0%, 3%]

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LOCF=last observation carried forward, LS=least squares
a. The p-value was obtained from a Fisher's exact test comparing active treatment to placebo.

The average percentage with ≥1 culture-verified AVVC episode through Week 48 was lower in the oteseconazole group compared with the placebo group in the ITT population by each sensitivity analysis method.

The between-group differences were statistically significant (p<0.001) when subjects with missing data were counted as failures, for subjects without any missed visits, and when subjects who took medication known to treat VVC were counted as failures (missing values were imputed using MI).

Table 11: Sensitivity Analyses: Proportion of Subjects with at Least 1 Culture-Verified Acute VVC Episode during the Maintenance Phase (ITT Population)

≥1 Culture-verified Acute VVC Episode Sensitivity Analysis Method	Oteseconazole (N=218)	Placebo (N=108)
Kaplan-Meier estimates of proportion with discontinuations censored at last visit [a]		
n (censored)	213 (205)	107 (68)
Percent	4.8%	38.9%
95% CI	2.3%, 9.8%	30.1%, 49.3%
Kaplan-Meier estimates of proportion with subjects censored at time of missing data [b]		
n (censored)	212 (204)	107 (68)
Percent	5.0%	39.1%
95% CI	2.3%, 10.4%	30.3%, 49.5%
Subjects with missing data counted as failures [c]		
n (%)	46 (21.1%)	52 (48.1%)
95% CI	15.9%, 27.1%	38.4%, 58.0%
P-value	<0.001	
Subjects without any missing visits [d]		
n/number included in analysis (%)	8/180 (4.4%)	39/95 (41.1%)
95% CI	1.9%, 8.6%	31.1%, 51.6%
P-value	<0.001	
Subjects who took medication known to treat VVC counted as failures, missing values imputed using MI [e]		
Average Percentage	21.3%	49.7%
Min, Max Percentage	21.1%, 22.0%	48.1%, 53.7%
P-value	<0.001	

Abbreviations: CI=confidence interval; COVID-19=coronavirus disease of 2019; ITT=intent-to-treat; MI=multiple imputation; VVC=vulvovaginal candidiasis

a. Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified acute VVC episode were censored at the last nominal visit for which they had signs and symptoms and culture data. Subjects who had missing data at any point prior to Week 48 and had both nonmissing signs and symptoms and culture data at Week 48 were censored at Week 48.

b. Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified acute VVC episode were censored at the last nominal visit for which they had signs and symptoms and culture data. Subjects who had missing data at any point prior to Week 48 that was not due to COVID-19 were censored at the last nominal visit before the first visit with missing signs and symptoms and culture data not due to COVID-19. Subjects who reached Week 48 without a culture-verified acute VVC episode and without any missing data were censored at Week 48.

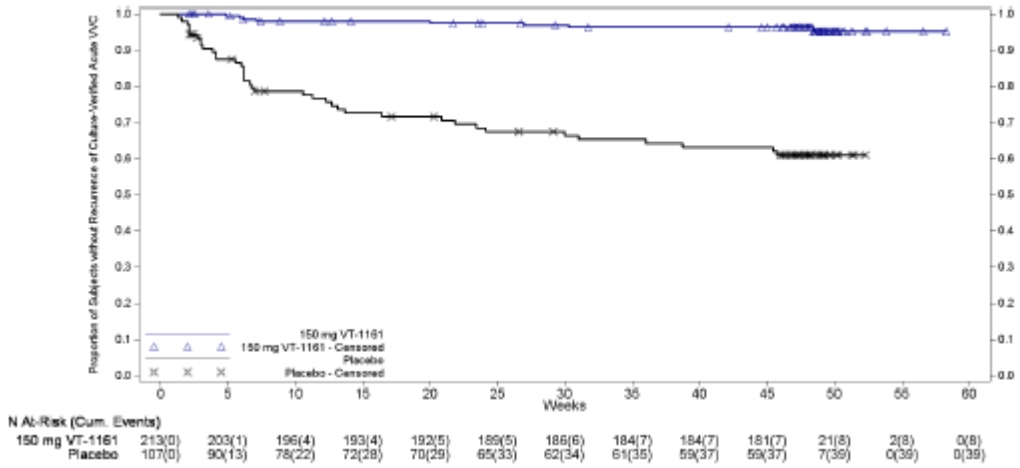
c. Subjects who discontinued the study prior to Week 48 without experiencing a culture-verified acute VVC episode were counted as having an episode at the time of discontinuation. Subjects who had missing data at any point prior to Week 48 not due to COVID-19 were counted as having an episode at the last nominal visit before the first visit with missing signs and symptoms and culture data. Subjects who reached Week 48 without a culture-verified acute VVC episode and without any missing data not due to COVID-19 were counted as not having a recurrence. 95% CI was calculated using an exact method (Clopper-Pearson). The p-value was from a Chi-square test.

Screening signs and symptoms score was not a statistically significant factor for predicting whether a subject had a relapse during the 48 weeks following clearance of an acute infection (p=0.656 in the ITT Population).

After controlling for the number of historic VVC episodes, oteseconazole was superior to placebo with reference to the average percentage with ≥1 culture-verified AVVC episode through Week 48 (p<0.001) in the ITT Population. In the oteseconazole group 78% of subjects had no instances of treatment with a known treatment for VVC during the Maintenance Phase compared with 54% of subjects in the placebo group.

The Kaplan-Meier plot indicates that most recurrences occurred during or shortly after completion of the 12-week treatment course.

Figure 3: Kaplan-Meier Plot of Time to First Recurrence of a Culture-verified Acute VVC Episode (ITT Population)



The average percentage of subjects with ≥1 positive culture for *Candida* species during the Maintenance Phase (i.e. regardless of signs and symptoms scores) was lower in the oteseconazole group (27.6%) compared with the placebo group (84.0%).

Table 17: Proportion of Subjects with at Least 1 Positive Culture for *Candida* Species during the Maintenance Phase (ITT Population)

≥1 Positive Culture (Missing value imputed with MI) [a]	Oteseconazole (N=218)	Placebo (N=108)
Average Percentage	27.6%	84.0%
Minimum, Maximum Percentage	26.6%, 28.9%	79.6%, 86.1%
P-value [b]	<0.001	

Abbreviations: ITT=intent-to-treat; MI=multiple imputation; VVC=vulvovaginal candidiasis
a. Missing values were imputed with MI using the following auxiliary information: region, treatment, baseline body mass index, baseline age, ethnicity, and visit.
b. The p-value was obtained using a Chi-square test comparing active treatment to placebo.

The average percentage of ITT subjects with ≥1 culture-verified AVVC episode through Week 12 was 1.8% for oteseconazole and 26.6% for placebo (p<0.001) and through Week 24 the average percentage remained lower in the oteseconazole group (2.8%) compared with the placebo group (31.9%).

The average percentage with ≥1 signs and symptoms score ≥3 (regardless of culture results) was 28.5% in the oteseconazole group vs. 50.8% in the placebo group (p<0.001). Mean changes and LS mean changes from Screening in the SF-36 MCS and in the SF-36 total score were similar between the treatment groups.

3.3.4.3. Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy.

Table 1. Summary of efficacy for trial VMT-VT-1161-CL-011

Title: A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oteseconazole Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis (RVVC)			
Study identifier	Protocol Number: VMT-VT-1161-CL-011 ClinicalTrials.gov Identifier: NCT03562156 EudraCT Number: 2018-001269-18		
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral oteseconazole capsules in the treatment of subjects with RVVC.		
	Duration of main phase:		48 weeks
Hypothesis	Superiority		
Treatments groups	Oteseconazole		Treatment: Oteseconazole Duration: 12 weeks Number randomised: 217
	Placebo		Treatment: Placebo Duration: 12 weeks Number randomised: 109
Endpoints and definitions	Primary endpoint		The proportion of subjects with 1 or more culture-verified acute VVC (aVVC) episodes during the Maintenance Phase (MP) in the Intent-to-Treat (ITT) Population. MP was postrandomisation through Week 48 AVVC (recurrence) was defined as a positive culture for Candida species and a clinical signs and symptoms score of ≥3.
	Secondary endpoint 1		Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase
	Secondary endpoint 2		Proportion of subjects with ≥1 positive culture for Candida during the Maintenance Phase
Database lock	Initial Database Lock: 30 November 2020 Final Database Lock 02 December 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (N=326) defined as all randomised subjects time point: postrandomisation through week 48 of the study		

Descriptive statistics and estimate variability	Treatment group	Oteseconazole	Placebo
	Number of subjects	217	109
	Primary endpoint (Average percentage) (minimum, maximum percentage)	6.7% 6.5%, 7.4%	42.8% 41.3%, 45.0%
Effect estimate per comparison	**Primary endpoint**	Comparison groups	Oteseconazole to Placebo
		P-value (Chi-square test)	<0.001
Analysis description	**Secondary analysis**		
Analysis population	ITT population		
Descriptive statistics and estimate variability	Treatment group	Oteseconazole	Placebo
	Number of subjects	217	109
	Secondary 1 [n (censored)] [Median (95% CI)	212 (198) Not estimable (NE,NE)	106 (61) NE (32.6,NE)
	Secondary 2 (Average percentage) (minimum, maximum percentage)	29.4% 27.6%, 33.6%	84.2% 81.7%, 87.2%

Table 2. Summary of efficacy for trial VMT-VT-1161-CL-012

Title: A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Oteseconazole Oral Capsules in the Treatment of Subjects with Recurrent Vulvovaginal Candidiasis		
Study identifier	Protocol Number: VMT-VT-1161-CL-012 ClinicalTrials.gov Identifier: NCT03561701 EudraCT Number: 2018-001270-26	
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral oteseconazole capsules in the treatment of subjects with RVVC	
	Duration of main phase:	48 weeks
Hypothesis	Superiority	
Treatments groups	Oteseconazole	Treatment: Oteseconazole Duration: 12 weeks Number randomised: 220
	Placebo	Treatment: Placebo Duration: 12 weeks Number randomised: 110

Endpoints and definitions	Primary endpoint		The proportion of subjects with 1 or more culture-verified acute VVC episodes during the Maintenance Phase in the Intent-to-Treat (ITT) Population. See CL-011
	Secondary endpoint 1		Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase
	Secondary endpoint 2		Proportion of subjects with ≥1 positive culture for Candida during the Maintenance Phase
Database lock	Initial Database Lock 30 Nov 2020 Final Database Lock 01 Dec 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (N=326) time point: postrandomisation through week 48 of the study		
Descriptive statistics and estimate variability	Treatment group	Oteseconazole	Placebo
	Number of subjects	218	108
	Primary endpoint (Average percentage) (Minimum, maximum percentage)	3.9 % 3.7%, 4.6%	39.4 % 38.0%, 42.6%
Effect estimate per comparison	**Primary endpoint**	Comparison groups	Oteseconazole to placebo
		P-value (Chi-square test)	<0.001
Analysis description	**Secondary analysis**		
Analysis population	Intent to treat (N=326)		
Descriptive statistics and estimate variability	Treatment group	Oteseconazole	Placebo
	Number of subjects	218	108
	Secondary 1 [n (censored)] [Median (95% CI)	213 (205) Not estimable	107 (68) Not estimable
	Secondary 2 (Average percentage) (minimum, maximum percentage)	27.6% 26.6%, 28.9%	84.0% 79.6%, 86.1%

Table 3. Summary of efficacy for trial VMT-VT-1161-CL-017

Title: A Phase 3, Randomised, Double-Blind Study to Evaluate the Efficacy and Safety of Oteseconazole Oral Capsules versus Fluconazole and Placebo in the Treatment of Acute Vulvovaginal Candidiasis Episodes in Subjects with Recurrent Vulvovaginal Candidiasis			
Study identifier	Protocol Number: VMT-VT-1161-CL-017 ClinicalTrials.gov Identifier: NCT03840616		
Design	Multicentre, randomised, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of oral oteseconazole capsules versus fluconazole and placebo in the treatment of acute VVC episodes in subjects with RVVC.		
	Duration of main phase:		50 weeks
Hypothesis	Non-inferiority and superiority		
Treatments groups	Oteseconazole		Treatment: Oteseconazole 600 mg on Day 1 and 450 mg on Day 2, then Maintenance doses of 150 mg once weekly for 11 weeks Duration: 12 weeks Number randomised: 147
	Fluconazole		Treatment: Fluconazole/Placebo 3 doses of 150 mg fluconazole every 72 hours, then placebo once weekly for 11 weeks Duration: 12 weeks Number randomised: 72
Endpoints and definitions	Primary endpoint		Proportion of subjects with ≥1 culture-verified acute VVC episode post randomisation through Maintenance Phase Week 48
	Secondary 1		Proportion of subjects with resolved acute VVC infections (clinical signs and symptoms score of <3) at Day 14 following treatment with oteseconazole or fluconazole/placebo
	Secondary 2		Proportion of subjects with ≥1 culture-verified acute VVC episode with signs and symptoms score of ≥3 during the Maintenance Phase (post Day 14 through Week 50)
	Secondary 3		Time to first recurrence of a culture-verified acute VVC episode with signs and symptoms score ≥3 during the Maintenance Phase (post Day 14 through Week 50)
	Secondary 4		Proportion of subjects with ≥1 positive culture for Candida during the Maintenance Phase (post Day 14 through Week 50)
Database lock	Initial/Final Database Lock 22 Dec 2020		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population	Intent to treat (N=219)		
Descriptive statistics and estimate variability	Treatment group	Oteseconazole	Fluconazole
	Number of subjects	147	72
	Primary endpoint (average percentage) Minimum, maximum percentage	 5.1% 4.1%, 6.8%	 42.2% 40.3%, 45.8%
Effect estimate per comparison	**Primary endpoint**	Comparison groups	Oteseconazole with fluconazole/placebo
		P-value (Chi-square test)	<0.001
Analysis description	**Secondary analysis**		
Analysis population	Intent to treat (N=219)		
Descriptive statistics and estimate variability	Treatment group	Oteseconazole	Fluconazole
	Number of subjects ITT	147	72
	Secondary 1 (Average percentage) Min, Max Percentage	Induction phase PP 93.1% 93.1%, 93.1%	Induction Phase PP 98.3% 98.3%, 98.3%
	Secondary 2 (Average percentage) Min, Max Percentage	 3.8% 3.0%, 6.0%	 41.1% 38.5%, 44.6%
	Secondary 3 n (censored) Mean (SE) Median (95% CI)	 120 (116) 36.5 (0.45) NE, NE	 60 (36) 35.3 (2.08) 44.0, NE
	Secondary 4 (Average percentage) Min, Max Percentage	 23.6% 21.1%, 27.1%	 79.7% 76.9%, 84.6%
Effect estimate per comparison	**Secondary 1**	Comparison groups	Oteseconazole with fluconazole/placebo
		95% CI	-10.7, 0.2%
		P-value	-

3.3.4.4. Clinical studies in special populations

Due to the indications sought, with infections that very predominantly occur in pre-menopausal women, oteseconazole has not been evaluated in subjects aged >65 years. The minimum age of the female subjects who were treated in Phase 3 studies was 16 years.

3.3.4.5. Analysis performed across trials (pooled analyses and meta-analysis)

The *Summary of Clinical Pharmacology* provides an overall view of the in-vitro susceptibility of clinical isolates from sponsored studies to oteseconazole. To focus on the Phase 3 studies, the following table provides an overview of oteseconazole and fluconazole MICs. However, it should be noted that the ranges do not specify oteseconazole MICs above 0.25 mg/L. Also, it is not specified how many isolates are from baseline samples or were obtained at other time points.

Table 2.7.2-41. Oteseconazole Activity against Clinical Isolates Derived from Phase III RVVC Studies

Clinical isolates	Oteseconazole			Fluconazole		
	Range (µg/mL)	MIC_{50} µg/mL	MIC_{90} µg/mL	Range (µg/mL)	MIC_{50} µg/mL	MIC_{90} µg/mL
Candida spp.						
• *C. albicans*	≤0.0005->0.25	0.004	0.06	<0.06-16	0.25	8
• *C. glabrata*	0.002->0.25	0.03	0.125	0.125-16	2	8
• *C. parapsilosis*	0.002-0.125	0.008	0.015	0.125-4	0.25	1
• *C. tropicalis*	0.004-0.015	0.004	0.015	0.125-32	0.5	1
• *C. lusitaniiae*	<0.001->0.25	0.03	0.25	≤0.06-16	0.125	8
Saccharomyces cerevisea	0.004->0.25	0.06	>0.25	0.5-16	2	16
Other species	≤0.0005->0.25	0.015	0.125	≤0.06->32	0.5	8
All isolates	≤0.0005->0.25	0.004	0.06	≤0.06->32	0.25	8

Applicant's dose rationale

Based on the MIC values and efficacy endpoints from CL-017, CL-012 and CL-011, the applicant opines that an oteseconazole plasma concentration of ~ 2 µg/mL should be clinically effective for treating AVCC and ~ 1 µg/mL should be clinically effective for preventing recurrence.

Mean plasma concentrations at day 14 following a loading dose regimen of 600 mg on Day 1 and 450 mg on Day 2 were slightly lower than those observed following the loading dose regimen of 150 mg QD for 7 days used in CL-012 and CL-011. The applicant considered that the two loading dose regimens are equivalent in terms of the resulting exposure to oteseconazole. The higher exposures in CL-012 and CL-011 could reflect the lower mean body weight at baseline (67.2 and 67.5 kg, respectively) compared to that in CL-017 (76.9 kg).

Table 2.7.3-66: CL-017, CL-012, CL-011, CL-006: Oteseconazole Plasma Concentrations

Study	Oteseconazole Dosing Regimen	Day 14 Plasma Concentration (µg/mL) Mean (SD)	Maintenance Phase Week 12 [a] Plasma Concentration (µg/mL) Mean (SD)
CL-017	600 mg on Day 1 and 450 mg on Day 2, followed by 150 mg QW for 11 weeks	1.4 (0.7)	2.7 (1.3)
CL-012	150 mg QD for 7 days, followed by 150 mg QW for 11 weeks	1.8 (0.7)	3.6 (1.5)
CL-011	150 mg QD for 7 days, followed by 150 mg QW for 11 weeks	1.7 (0.9)	3.4 (2.0)
CL-006	150 mg QD for 7 days, followed by 150 mg QW for 11 weeks	1.4 (0.7) [b]	2.6 (1.4)

Abbreviations: QD=once daily; QW=once weekly; SD=standard deviation

a. Week 14 in CL-017 and Week 12 in CL-012/CL-011 are both post 11 weeks of 150 mg QW dosing, i.e., at the end of Maintenance Phase in all 3 studies.

b. Day 7 plasma concentration; Day 14 was not assessed in CL-006.

To assess the variability in oteseconazole exposure from the dosing regimen in relation to outcome, an analysis was performed whereby quartiles of Day 14 exposure (bins) were created. The likelihood of subjects in these exposure bins experiencing recurrence of a culture-verified AVVC episode was determined by a logistic regression analysis on the primary endpoint of proportion of subjects with ≥1 culture-verified AVVC episode during the Maintenance Phase and by calculating the hazard ratio for the time to recurrence (secondary endpoint).

In these analyses, the outcomes for each quartile bin were compared with the BLQ bin (i.e. subjects who had no plasma concentration of oteseconazole). For the hazard ratio, the higher quartile bins were also compared with the lower quartile bins. The hazard ratio was low regardless of the subject's Day 14 exposure. However, the subjects in the lowest exposure quartile had a slightly higher likelihood of recurrence compared with subjects in the higher quartiles.

The analysis on the primary endpoint was highly significant for all exposure quartiles. Based on these data, the loading dose/maintenance dose regimen provides oteseconazole exposures that are effective even when accounting for the inter-subject variability in oteseconazole exposure.

Table 2.7.3-67: CL-017, CL-012, and CL-011 Integrated Pool, RVVC Prevention, PK/Response Analysis: Time to First Recurrence of Culture-Verified Acute VVC Episode During the Maintenance Phase - (Safety and Maintenance Phase ITT)

Time to First Recurrence of Culture-Verified Acute VVC (Weeks) [a]	Concentration Bin Group				
	A (0, 1080]	B (1080, 1670]	C (1670, 2200]	D (2200, 4260]	E (BLQ]
n (censored) [b]	120 (110)	123 (117)	125 (123)	125 (121)	294 (184)
Median (95% CI) [b]	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q1, Q3 [b]	NE, NE	NE, NE	NE, NE	NE, NE	19.0, NE
Versus Bin E					
p-value [c]	<0.001	<0.001	<0.001	<0.001	—
Hazard Ratio [d]	0.17	0.10	0.03	0.06	—
95% CI [d]	0.09, 0.33	0.04, 0.23	0.01, 0.13	0.02, 0.17	—
p-value [d]	<0.001	<0.001	<0.001	<0.001	—
Versus Bin A					
p-value [c]	—	0.266	0.015	0.082	—
Hazard Ratio [d]	—	0.65	0.27	0.57	—
95% CI [d]	—	0.21, 1.94	0.05, 1.49	0.12, 2.78	—
p-value [d]	—	0.437	0.132	0.487	—
Versus Bin B					
p-value [c]	—	—	0.149	0.519	—
Hazard Ratio [d]	—	—	0.35	0.73	—
95% CI [d]	—	—	0.06, 1.89	0.14, 3.71	—
p-value [d]	—	—	0.220	0.705	—
Versus Bin C					
p-value [c]	—	—	—	0.399	—
Hazard Ratio [d]	—	—	—	1.94	—
95% CI [d]	—	—	—	0.25, 15.02	—
p-value [d]	—	—	—	0.526	—

Time to First Recurrence of Culture-Verified Acute VVC (Weeks) [a]	Concentration Bin Group				
	A (0, 1080]	B (1080, 1670]	C (1670, 2200]	D (2200, 4260]	E (BLQ]

Abbreviations: BLQ=below limit of quantitation; CI=confidence interval; ITT=Intent to Treat (Population); NE=not estimable; OTE=oteseconazole; PK=pharmacokinetic; Q=quartile; RVVC=recurrent vulvovaginal candidiasis; VVC=vulvovaginal candidiasis

a. Recurrence was defined as a clinical signs and symptoms score ≥3 and a positive culture for Candida. Subjects without a recurrence were censored at their last nonmissing assessment during the Maintenance Phase.

b. Kaplan-Meier estimates

c. The p-value was obtained from a log-rank test comparing each OTE concentration bin group to the reference bin group. The 5 OTE concentration bin groups were based on OTE concentration at Day 14 and were defined as BLQ, (0, Q1], (Q1, Q2], (Q2, Q3], and (Q3, Q4].

d. Hazard ratio, 95% CI for hazard ratio, and p-value were from a Cox regression model with factors for OTE concentration bin group, region, baseline body mass index, baseline age, ethnicity, and Screening signs and symptoms score.

3.3.5. Discussion on clinical efficacy

The applicant's revised proposed indications are:

Vivjoa is indicated for the prevention of acute vulvovaginal candidiasis (AVVC) in adult female patients of non-childbearing potential who have a history of RVVC (see sections 4.3, 4.6, 5.1 and 5.3).

Vivjoa is indicated for prevention of acute vulvovaginal candidiasis (AVVC) in adult female patients with no childbearing potential who have a history of recurrent vulvovaginal candidiasis (RVVC). See sections 4.3, 4.6, 5.1 and 5.3.

The applicant's proposed posology is:
1. 600 mg on Day 1, 450 mg on Day 2
2. 150 mg QW for 11 weeks starting on Day 14

This exact posology was evaluated only in CL-017, in which the 2-day treatment regimen also served as the loading dose regimen for the subsequent weekly preventive regimen. In studies CL-011 and CL-012, the screening AVVC episode was treated with fluconazole (3 x 150 mg doses given 72 h apart). The maintenance oteseconazole regimen commenced after randomisation into the study at ~14 days after the first dose of fluconazole, starting with 150 mg QD for one week and then weekly dosing with 150 mg for 11 weeks starting on day 14 post-randomisation.

Design and conduct of clinical studies'

Definitions of AVVC and RVVC in Phase 2 and 3 clinical studies

History of RVVC
In the dose-finding study CL-006 and in the three Phase 3 studies CL-011, -012 and -017, subjects were to have a history of RVVC, which was defined as having ≥3 AVVC episodes in 12 months prior to screening, including the presenting episode at screening. Due to variable record keeping and presentation to medical facilities during prior episodes, specific criteria to define the qualifying episodes that occurred prior to the screening visit episode could not be applied. This limitation was acknowledged in prior CHMP scientific advice, at which time it was accepted for reasons of study feasibility. However, at least one of the pre-screening AVVC episodes was to have been documented with any of a positive culture, PCR, Affirm test, KOH, Pap, or other FDA-approved diagnostic test.

Definition of the presenting episode of AVVC
The presenting episode of AVVC was defined by a composite signs and symptoms score of ≥3 along with a positive Gram's stain and/or a KOH wet mount preparation from a vaginal smear suggesting presence of Candida. Since the score was determined from applying a 0-3 scale to six signs and symptoms, it was possible that a subject with just one severe sign or symptom could meet the study selection criteria. This issue was discussed at the time of CHMP advice, when a higher score was suggested, for establishing eligibility. Using a low score for eligibility also has implications for the definition of resolution (see below). Furthermore, since only a positive microscopy was required, subjects did not necessarily have Candida confirmed from screening visit cultures. In fact, in CL-017 only 40% had screening cultures positive for *C. albicans* and 2% had cultures positive for *C. glabrata*. The respective rates in CL-011 were 51% and 6% and those in CL-012 were 50% and 5%. This matter is discussed further below (see analysis populations).

Resolution of the presenting AVVC episode

- In CL-006, -011 and -012, clinical resolution of the presenting AVVC episode was evaluated on ~day 14 after start of induction treatment of all subjects with three doses of 150 mg fluconazole given 72 h apart. Only subjects considered to have clinical resolution of the presenting AVVC episode (score <3) were eligible for enrolment, with randomisation to receive oteseconazole (150 mg QD for 7 days and 150 mg QW for 11 weeks) or matching placebo.
- In CL-017, resolution of the baseline AVVC episode was evaluated on ~day 14 after the start of randomised treatment with either oteseconazole (600 mg day 1 and 450 mg day 2) or fluconazole (same regimen as in the other studies). Only subjects considered to have clinical resolution of AVVC (score <3) were eligible for continuation into the maintenance phase, in which they received oteseconazole if they had been initially randomised to oteseconazole and placebo if they had been initially randomised to fluconazole.

Thus, in all three Phase 3 studies, there was no requirement for a negative microscopy or negative culture for Candida (in the subset with a positive screening culture) to determine resolution of the presenting AVVC. Resolution of the presenting AVVC episode required only a clinical score <3 and only subjects with clinical resolution (score <3) were eligible for entry into the maintenance phase and, thus, for evaluation of the effect of maintenance treatment on the recurrence rate. Due to requirement of a score ≥3 to define the presenting AVVC episode, the CHMP recommended that clinical resolution of AVVC should require achievement of a score of zero or 1.
Since this advice was not followed, it is of interest to look at the recurrence rates for those who did achieve a score of zero on day 14 after start of treatment for the presenting AVVC episode.

Primary endpoint in Phase 3 studies
The definition of a recurrence (i.e. a new episode of AVVC) in the Maintenance Phase required a positive fungal culture for *Candida* species associated with a clinical signs and symptoms score ≥3. The CHMP considered this acceptable since the low score for the clinical definition was viewed as providing a conservative estimate of efficacy.

Prevention of recurrence of AVVC in subjects with a history of RVVC

Oteseconazole dose regimen selected for Phase 3
The dose-finding study CL-006 compared four oteseconazole 12-week regimens with placebo for prevention of recurrence in a population similar to that which was later enrolled into Phase 3 studies. Moreover, the stated primary endpoint was the same as in the Phase 3 studies. There was no rationale provided for initiating treatment in CL-006 with 7 once daily doses of oteseconazole before moving to once weekly dosing. The rationale given for comparing 150 and 300 mg dose levels was based on the AVVC study (CL-004), from which the applicant concluded that plasma exposures ~1 µg/mL should be clinically effective. The applicant expected that 150 mg and 300 mg given QD for 7 days and then QW would result in Cmin of ~1 µg/mL and ~2.5 µg/mL, respectively.

In CL-006, with just over 40 randomised subjects per group, all the oteseconazole regimens statistically significantly reduced the percentage of subjects with at least one recurrence over 48 weeks, with no discernible benefit for 300 mg over 150 mg or for 24 weeks over 12 weeks of treatment. Almost all the recurrences occurred in the first 12 weeks. The sensitivity analyses supported the primary analysis. Moreover, the results in the mITT (negative KOH and *Candida* culture and zero symptom score at randomisation) and mITT3 (screening positive culture for Candida and a score of ≥3 with negative KOH and *Candida* culture with zero symptom score at baseline) populations supported the primary analysis.

At the time of CHMP scientific advice that addressed the design of CL-011 and -012, the CHMP agreed that this Phase 2 study suggested that there was no apparent benefit for the 300 mg dose over the 150 mg dose or for 24 weeks over 12 weeks of dosing for prevention of recurrence of VVC. The need for a loading dose regimen that comprised 7 daily doses of 150 mg oteseconazole was unclear.

Design of Phase 3 studies

As indicated above, the selection criteria based on history of RVVC and the presenting AVVC episode were comparable across the studies. The exclusion criteria were appropriate.

The use of a placebo control in the maintenance phase was discussed in the 2018 CHMP advice and it was agreed that showing superiority over placebo would be acceptable evidence of efficacy. Moreover, it was recognised that it would be very difficult to justify a non-inferiority margin to apply to a study design that compared weekly oteseconazole with weekly fluconazole. Moreover, although a weekly fluconazole regimen was recommended for prevention of recurrences in women with RVVC in various guidelines in 2018, this was not reflected in the brand leader SmPC until 2020.

In each study, the weekly maintenance regimen of 150 mg oteseconazole or placebo commenced at 14 days after start of treatment for the qualifying AVVC episode.
The difference was that CL-011 and -012 employed a loading dose regimen of 150 mg QD for 7 days whereas CL-017 used a 2-day loading regimen of 600 mg and 450 mg also intended to treat the presenting AVVC episode. In each study, weekly dosing started on day 14 after the first loading dose.

Primary efficacy outcome measure

The primary efficacy outcome measure as stated in the three SAPs was the proportion of subjects with 1 or more culture-verified AVVC (see definition above) episodes during the Maintenance Phase in the ITT population (all randomised, i.e. including those without positive screening cultures). However, there was a difference between studies in the Maintenance Phase because of timing of randomisation:

- In CL-011 and -012, randomisation (2:1) to oteseconazole or placebo occurred after confirming clinical resolution of the presenting AVVC at a visit held ~ 14 days following open-label treatment of the screening episode with fluconazole. Recurrences were counted from time of randomisation to week 48.

- In CL-017, subjects with a qualifying AVVC episode were randomised (2:1) to oteseconazole (600 mg on day 1 and 450 mg on day 2) or fluconazole (as in CL-011 and -012), followed by 48 weeks of once weekly oteseconazole or placebo, respectively, for maintenance. Recurrences were counted from time of randomisation to week 50. However, only those subjects with a score <3 at the ~day 14 visit received their assigned maintenance regimen. Subjects who still had a score of at least 3 at the ~day 14 visit were considered as having failed the induction phase and were not continued into the maintenance phase.

Essentially, then, the evidence to support the ability of oteseconazole (loading regimen followed by 150 mg QW) to reduce the rate of recurrence comes from a population with clinical resolution of the presenting AVVC episode (defined by signs and symptom score reduction to <3) following an initial treatment regimen.

While study CL-017 counted recurrences from baseline, i.e. regardless of whether subjects had a clinical response to treatment of the presenting AVVC episode, recurrences beyond day 14 were captured only for those who did have a clinical response at day 14 since only these subjects entered the maintenance phase. Furthermore, recurrences within 14 days of randomisation could occur only in

subjects who did respond to initial treatment but then had a recurrence before the day 14 visit. Not only is it doubtful that this would have been detected as a separate (i.e. new) episode of AVVC but also there do not seem to be any criteria applied in terms of a time gap that might differentiate the presenting AVVC episodes from any early recurrent episodes of AVVC.

In CL-011 and -012, case ascertainment (i.e. detection of recurrences) occurred at scheduled visits at weeks 2, 6, 12 (end of treatment), 18, 24, 30, 36, 42 and 48 (counting from randomisation). In CL-017, case ascertainment occurred at scheduled visits at weeks 2 (test of cure for acute treatment), 8, 14 (end of treatment), 20, 26, 32, 38, 44 and 50 (counting from randomisation). The study schedules indicate that "Unscheduled visits" were to occur if a recurrence was suspected by the subject. It was left entirely to the subjects to determine if they thought they had a recurrence in between scheduled visits, in which case an unscheduled visit was to be organised and completed.

Analysis populations

In contrast to the ITT population used for the primary analysis, inclusion in the mITT population required a positive culture at screening and a negative culture after treatment of the presenting AVVC episode. This population is of interest since these subjects had AVVC associated with Candida at presentation and had responded both clinically and mycologically to treatment for AVVC before they commenced their maintenance regimen.

Sample size calculations

For all three Phase 3 studies, the sample size for the purposes of analysing the recurrence rates was based on an assumed rate of 50% in the placebo group and a treatment difference of 35%. These assumptions were justifiable from the results of CL-006. CL-011 and -012 were sized to provide 95% power based on a 2-sided alpha =0.05. The plan to conduct two identical studies, each with standard alpha, was considered acceptable at the time of CHMP advice.

However, the planned sample sizes for CL-011 and -012 were much larger than needed to address the primary endpoint because they were determined to provide 80% power to detect a treatment difference of 3.9 between the oteseconazole and placebo groups in the change from Screening through Week 48 in the SF-36 MCS with an SD of 10 points. It was estimated that 240 subjects (160:80) were needed and, due to the expected discontinuation rate, approximately 300 subjects were planned.

CL-017 was not planned at the time of the 2018 CHMP advice. The sample size calculation was driven by the secondary endpoint (see under *Treatment of AVVC* below).

Analysis of the primary endpoint

At the time of the CHMP advice on clinical development in 2018, only studies CL-011 and -012 were planned.

At that time, the applicant proposed that a multiple imputation (MI) statistical approach be employed for the handling of missing data for the primary efficacy endpoint. In order to impute the missing values, a set of common subject characteristics (i.e. region, treatment, visit, baseline BMI, age at baseline and ethnicity) were to be included in the imputation model. The applicant proposed to use these characteristics to provide unbiased estimates for the missing data points for the culture result and/or the signs and symptoms score in a single model to produce a complete dataset. This would be done 10 times and then the endpoint would be derived for each of the 10 complete data sets and those 10 complete datasets would be analysed using standard procedures for complete data and the 10 results would be combined to produce a single p-value.

In response, the CHMP noted that MI is based on the assumption of missing at random, which might be questionable for the Phase 3 trials. Specifically, whether or not data were truly missing at random could not be ascertained and it could be deemed unlikely. Nevertheless, the applicant persisted with the plan to use MI and this was reflected in the SAPs for the analyses of the recurrence rates in all three Phase 3 studies. Section 3.4.4 of each SAP describes the planned analysis with MI (see description of studies in section 3), but in limited detail. This explains why the applicant's tables that show the analysis of the primary endpoint and the sensitivity analyses, as well as many of the tables concerning secondary endpoints, report the *average percentage*.

The CSRs present analyses of the primary endpoint as defined in the SAPs, i.e. in which missing values have been handled using MI. The term "average percentage" equates with the estimate of the proportion of subjects with an event in each treatment group under a particular assumption about the missing data at end of the maintenance phase. The figures provided for the primary analyses show the means of the proportions of subjects with an event by end of maintenance phase in each of the 10 imputed datasets.

The approach taken relies on the plausibility of the Missing at Random assumption. This assumes that the recurrence rate in subjects who dropped out was similar to that observed in similar subjects in the same treatment arm who remained in the study and is not verifiable. Moreover, it seems unlikely that dropouts in the oteseconazole arm and those remaining on study in the placebo arm would experience similar recurrence rates, noting that the recurrence rate was not stable over time. That is, in the Phase 2 and in all three Phase 3 studies it was a consistent finding that most of the first recurrences occurred early on in the studies, mainly during or shortly after completion of the 12-week treatment periods.

Further consideration of the plausibility of the missing data assumptions is important. While it appears there would be a statistically significant treatment effect under all but the most extreme missing data assumptions (i.e. all in the oteseconazole group and none in the placebo group have a recurrence by end of maintenance phase) there is substantial uncertainty regarding the magnitude of the treatment effect. For example, in CL-017, the point estimate for the difference in proportions between treatment groups could be as small as 11% or as large as 45% depending on how the missing data are handled. See further on this issue under the discussion of the results by study and consideration of observed event rates, i.e. data not subjected to MI.

It is noted that subjects who were treated for VVC on study without meeting the definition of a culture-verified AVVC were not treated as experiencing a recurrent episode in the primary analysis of the primary endpoint; this could have resulted in an anti-conservative estimate of efficacy.

Treatment of AVVC in subjects with a history of recurrent VVC (CL-017 induction phase)

<u>Oteseconazole and fluconazole dose regimen selection for CL-017</u>
CL-004 was a study of oteseconazole for treatment of AVVC. It was not conducted in women with a history of RVVC. Eligible subjects presented with an episode of AVVC with a combined score at least 6. It compared a single dose of 150 mg fluconazole (as approved for AVVC when not occurring in women with RVVC) with 3 consecutive days of oteseconazole (300 mg QD, 600 mg QD or 600 mg BID). Based on complete clinical resolution at Day 28, in very small numbers per group, oteseconazole regimens were at least similarly efficacious to fluconazole and data suggested a dose of at least 600 mg QD.

It is unclear how the applicant selected the regimen of 600 mg on day 1 and 450 mg on day 2 for treatment of AVVC in women with a history of RVVC in CL-017.

The applicant's clinical overview and summaries refer to a conclusion that an oteseconazole plasma concentration of approximately 2 µg/mL should be clinically effective for treating the acute *Candida* infection and approximately 1 µg/mL should be clinically effective for preventing recurrent episodes. However, this seems to be based solely on comparing mean plasma levels with MICs. See further below in the discussion of loading doses.

The 3-dose fluconazole regimen used for treatment of the AVVC episode in women with a history of RVVC in the Phase 2 (CL-006) and Phase 3 (CL-011, -012 and -017) studies is approved for this purpose in the EU SmPC for Diflucan 150 mg capsules. Therefore, it is acceptable as a comparative regimen for evaluating oteseconazole for treatment of AVVC in women with a history of RVVC.

Study design

Subjects with a history of RVVC and with a screening visit episode of AVVC were randomised to receive oteseconazole (600 mg on day 1 and 450 mg on day 2) or fluconazole (3 doses of 150 mg given 72 h apart) in a double dummy fashion. On ~day 14 from randomisation, subjects were assessed for resolution based on achieving a signs and symptoms score <3.

A primary objective of CL-017 was to compare the efficacy of oral oteseconazole and fluconazole in the treatment of an acute VVC episode in RVVC subjects but the proportion of subjects with resolved AVVC (clinical signs and symptoms score of <3) at Day 14 was a secondary endpoint. Despite this, the study sample size of 180 subjects (120 oteseconazole) was driven by the aim to provide at least 88% power to detect non-inferiority between oteseconazole and fluconazole based on a NI margin of 15% and a type 1 error rate of 0.05, assuming that 90% of fluconazole subjects had resolution of AVVC by day 14.

The applicant launched into a lengthy attempt to justify this NI margin, noting that this study was not planned at the time of CHMP advice in 2018 so there was no pre-agreement on the NI margin with the CHMP. While AVVC is certainly not life-threatening and does not have major sequelae, it can be very distressing and disruptive to normal functioning. Since fluconazole (3 doses of 150 mg 72 h apart) remains a highly effective treatment for AVVC in women with a history of RVVC, a new 2-dose treatment that results in a resolution rate as much as 15% lower than that of fluconazole is not considered acceptable.

The analysis of the day 14 clinical resolution rates was conducted in the induction phase PP population, defined as all randomised subjects with no deviations to inclusion/exclusion criteria that could affect treatment outcome at day 14, with ≥80% adherence and no major protocol violations. In a NI study, it would have been preferred that the ITT and PP populations were designated co-primary. The applicant did also define an induction phase mITT population, which was the subset with a positive culture at screening, and results in this subset are of interest. Also, the results for the ITT population are presented even though this was not a designated primary analysis population.

Efficacy data and additional analyses

Prevention of recurrence of AVVC in subjects with a history of RVVC

CL-017

Of the 219 subjects randomised to treatment (i.e. ITT population) there were 22/147 in the oteseconazole group and 9/72 in the fluconazole group who failed the induction phase (i.e. did not have the required clinical response of score <3 on day 14 after start of initial randomised treatment) so they did not enter the maintenance phase.

With a few others discontinuing early for other reasons, 185 entered the maintenance phase (123 oteseconazole and 62 placebo) and 167 completed the study (112 and 55 per group).

The average percentage with at least one recurrence of culture-verified AVVC (i.e. meeting the primary endpoint criteria) by week 50 (i.e. counting any recurrences from baseline so including any within 14 days of randomisation) was 5.1% in the oteseconazole group and 42.2% in the control group. When counting recurrences only from day 14 to week 50 (i.e. during the 48 weeks of the maintenance phase), the average percentages with culture-verified AVVC were 3.8% vs. 41.1%, respectively. When applying the applicant's MI approach and from the reported average percentages, oteseconazole 150 mg QW, started on day 14 after a 2-day treatment regimen, achieved a statistically significant reduction in the proportion of subjects with at least one culture-verified AVVC episode whether counting from randomisation (primary analysis) or from day 14 (secondary analysis). Almost all recurrences involved *C. albicans*.

The sensitivity analyses for the primary endpoint support the primary analysis counting proportions with recurrence from randomisation. Importantly, when subjects with missing data were counted as failures, the recurrence rate was 29.9% (Clopper Pearson 95% CI 22.7%, 38.0%) for oteseconazole vs. 55.6% (43.4%, 67.3%) for placebo, which was a statistically significant difference. Thus, over and above the concerns about the approach taken to the primary analysis, the worst-case recurrence rates (missing=failure, in which subjects with no recurrence before they discontinued were counted as having a recurrence at discontinuation) support a conclusion that oteseconazole prevents recurrences. Also supportive are the average percentages for recurrences that were derived when subjects who took any medication known to treat VVC were counted as failures (38.4% oteseconazole and 58.3% placebo; p=0.009).

These sensitivity analyses were repeated counting proportions with recurrence from day 14 for the 185 subjects who entered the maintenance phase. Again, when subjects missing data were counted as failures, the recurrence rates calculated using the ITT population numbers as denominators, were 22.6% for oteseconazole and 50.8% for placebo (p=<0.001).

The Kaplan-Meier plot supports the conclusion above that very few subjects were considered to have had a recurrence until 2-3 weeks after randomisation, with about half of all first recurrences occurring before end of the maintenance treatment phase (week 14 from randomisation) and the majority occurring before week 20.

The average percentages with scores ≥3 regardless of culture results were 43.3% for oteseconazole vs. 64.6% for placebo, with a statistically significant difference. The rates for positive cultures regardless of scores by visit in the ITT population were consistently higher than rates for the primary endpoint, such that by week 50 the cumulative percentages (from Table 14.2.3.2.1) were 22/120 (18%) for oteseconazole and 43/60 (72%) for placebo based on the numbers that attended the visit. Based on ITT denominators, the rates would be 15% vs. 60%. Since Candida *spp*. is commonly found in normal vaginal flora in specimens obtained from asymptomatic women, it is not surprising that rates for positive cultures exceeded those for protocol-defined culture-verified AVVC. However, it is noted that weekly oteseconazole suppressed detectable Candida in vaginal specimen cultures.

With a primary endpoint that was based on proportions with at least one recurrence of AVVC meeting the primary endpoint definition, but with resumption of assigned treatment in subjects who continued on study after treatment for the on study AVVC episode, there is also interest in the ability of weekly oteseconazole to reduce the total number of recurrences that met the primary endpoint definition.

The mean number of culture-verified episodes from day 14 to week 50 was lower in the oteseconazole group (0.0 [SD 0.18]) compared with the placebo group (0.8 [1.24]; p<0.001).

The CSR reports that 4 ITT subjects (3%) in the oteseconazole group had 1 culture-verified episode (i.e. those that did have a recurrence meeting the primary endpoint definition only had the one episode) while 14 (19%), 2 (3%), 6 (8%) and 2 (3%) ITT subjects in the placebo group had 1, 2, 3 or 5 culture-verified episodes, respectively. Also, in the ITT population, the mean number of times a subject was treated for VVC during the maintenance phase (noting that investigators could treat episodes that did not meet the full primary endpoint definition) was 0.7 in the oteseconazole group vs. 1.3 in the placebo group (p=0.043).

Finally, there is interest in the recurrence rates documented in:
a) The mITT population, which included only subjects with a positive screening culture who entered the maintenance phase with a negative culture on day 14. There were only 67 subjects in this population (46 oteseconazole and 21 placebo). The average percentages with recurrence were 0% in the oteseconazole group vs. 55.7% in the placebo group.

b) The sub-population that entered the maintenance phase with a zero signs and symptoms score on day 14. Table 13 in the CSR for CL-017 shows average percentages with recurrence up to week 50 for various subgroups, including subjects with a signs and symptoms score of 0, 1, or 2 at Day 14. This table indicates that 63 oteseconazole and 25 fluconazole group subjects had a score of zero on day 14 and average percentages with recurrence in this subset were 3.8% for oteseconazole vs. 52.8% for placebo.

CL-011 and CL-012

Since these studies were of identical design, and only subjects who had a clinical response to 3 doses of fluconazole were randomised into these studies to receive maintenance treatment with oteseconazole (150 mg daily for 7 days and then 150 mg weekly for 11 weeks) or placebo, the results of these studies are discussed together. As mentioned above, the sample sizes were much larger than necessary to address the primary endpoint. In contrast to CL-017, these studies were not confined to the US. In terms of RVVS history, baseline demographics and proportions with positive cultures at screening, the populations were similar and also comparable with that of CL-017.

Based on average percentages, the magnitude of treatment effect was comparable in these studies and both demonstrated a statistically significant difference in the recurrence rate between oteseconazole (6.7% in CL-011 and 3.9% in CL-012) and placebo (42.8% and 39.4%, respectively).

The planned sensitivity analyses of the primary endpoint support the primary analysis. In particular, in the worst-case sensitivity analysis, with Missing=Failure, the proportions with at least one protocol-defined recurrence were 25.8% vs. 51.4% in CL-011 and 21.1% vs. 48.1% in CL-012, which were statistically significant differences.

The tabulations of cumulative numbers with at least one recurrence meeting the primary endpoint definition also support the findings based on the calculated average percentages that used MI. In CL-011 there were 14 (7%) vs. 45 (42%) with recurrences by week 48. In CL-012 there were 8 (4%) vs. 39 (36%) with recurrences by week 48.

The Kaplan-Meier plots indicated that the majority of recurrences in the placebo groups occurred during the first 12-18 weeks. The majority of recurrences were associated with *C. albicans*.

For the subsets (just over half of the ITT population) in each study with a score of zero at randomisation, the average percentages with recurrence were 7.1% vs. 37.6% in CL-011 and 4.3% vs. 36.3% in CL-012.

Both studies showed lower rates of treatment with any agent for AVVC in the oteseconazole group. Also, lower proportions in the oteseconazole groups had at least one positive culture for Candida (i.e. regardless of symptom score) or a score ≥3 (i.e. regardless of culture) during the maintenance phase.

Dose of oteseconazole for prevention of recurrence

Administration of a weekly dose of 150 mg oteseconazole for 11 weeks, starting one week after completion of a loading dose regimen of 150 mg QD for 7 days, is supported by the consistent results of the two identical studies CL-011 and -012. The applicant's SmPC recommends that oteseconazole 150 mg QW is started on day 14 after dosing with 600 mg on day 1 and 450 mg on day 2. This 2-day starting regimen was intended for treatment of the presenting episode of AVVC in study CL-017 (on which see below) but, effectively, it also served as a loading dose for the weekly regimen that started on day 14. The applicant provided simulated plasma concentration-time profiles using the two loading dose regimens applied in Phase 3, suggesting no appreciable differences at day 14. On this basis, the simple 2-day loading regimen has been accepted.

Treatment of AVVC in subjects with a history of recurrent VVC

The evidence needed to support the use of this new antifungal agent to treat acute episodes of VVC in subjects with a history of RVVC was not discussed with the CHMP. The applicant provides a single study to support this, which is confined to an assessment of non-inferiority vs. a licensed regimen in ~200 female subjects. The evidence provided to support the use of 150 mg QW oteseconazole (after a suitable loading regimen) to prevent recurrences cannot be used to support the adequacy of the acute treatment regimen. Under such circumstances, two studies that demonstrate the efficacy of the treatment regimen would usually be required.

The evidence from CL-017 is not sufficiently compelling to support use of oteseconazole 600 mg and 450 mg on two consecutive days to treat AVVC in women with a history of RVVC.

On ~day 14 from randomisation, in the PP population that was designated primary, the average percentage (derived using the MI approach) with resolution of AVVC (clinical response based on achieving a signs and symptoms score <3), was 93.1% for oteseconazole vs. 98.3% for fluconazole, with Wald 95% CI -10.7%, 0.2%. On this basis, and with a pre-defined NI margin of -15%, the applicant claims that non-inferiority was demonstrated. This cannot be agreed since:

a) The lower bound of the 95% CI exceeds -10%, which is considered to be a more robust margin;
b) The applicant used the Wald method to calculate the CI, which tends to favour a demonstration of NI vs. other calculation methods;

Furthermore, in the PP population, when subjects with missing day 14 data were counted as failures or were excluded, the AVVC resolution rates were lower for oteseconazole (90.8% and 92.9%) vs. fluconazole (98.3% in both analyses) with lower 95% CI at -14.3 and -11.8.

In the ITT population the reported average percentages for day 14 clinical response are 93.2% vs. 95.8% with a lower bound of the Wald 95% CI at -8.8%.

The induction phase mITT population had a positive screening culture and comprised 100 subjects (46% of all oteseconazole and 48% of all fluconazole subjects). In this population, the average percentages for day 14 clinical response are 98.5% for oteseconazole vs. 94.1% for fluconazole, with a lower bound of the Wald 95% CI at -4.1%.

In addition, the average percentages that reached scores of zero at day 14 were slightly higher for oteseconazole in the PP, mITT and ITT populations, with lower bounds of the Wald 95% CI at -12.2, -6.6 and -5.4, respectively. The average percentages with clinical signs and symptoms of 0 plus negative cultures for *Candida* species at Day 14 were comparable between treatments. These findings are supportive of efficacy but they are based on a single study.

Comments on the mycological data obtained in Phase 3 studies

Not all subjects had a positive culture for Candida at screening. The primary endpoint in Phase 3 trials was culture-verified AVVC but additional subjects may have had positive cultures at various visits that were not accompanied by clinical scores ≥3. Unfortunately, the CSRs and the applicant's summaries of clinical pharmacology and efficacy report only MICs for all isolates, with no information on whether they are baseline or post-baseline or whether they were obtained at the time of meeting the primary endpoint or at another visit at which the subject had a positive culture but had a clinical score <3.

3.3.6. Conclusions on clinical efficacy

Conclusion on prevention of a recurrence in adult female patients with a history of RVVC

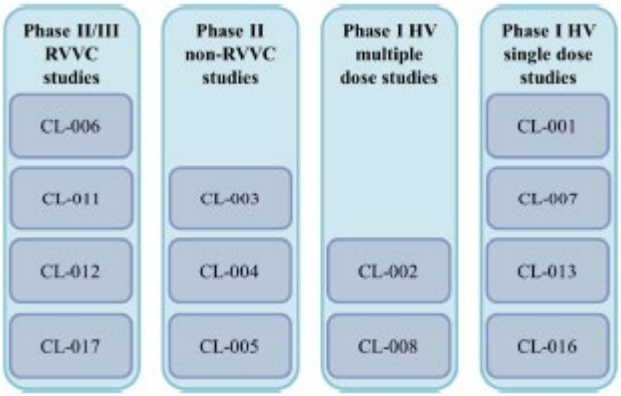
The three Phase 3 trials support the use of oteseconazole to reduce the risk of a recurrence of AVVC in women with a history of RVVC. While the applicant has taken a simplistic approach to selection of the recommended loading dose regimen, the advantages of a simple 2-day option are appreciated and the PK simulations support accepting this as the standard loading dose regimen.

Conclusion on treatment of AVVC in adult female patients with a history of RVVC

There is a Major Objection to the applicant's claim that oteseconazole 600 mg on day 1 and 450 mg on day 2 can be used to treat AVVC episodes in women with a history of RVVC. A single Phase 3 study has been conducted, which does not provide compelling evidence of efficacy. In this study, resolution of the presenting AVVC episode at day 14 was a secondary endpoint, although it is acknowledged that the study sample size was determined to address this endpoint.

3.3.7. Clinical safety

The most relevant data come from the 3 Phase 3 studies noting that only CL-017 used the final recommended loading dose regimen but all three used 150 mg weekly as the maintenance regimen. Some tables presented below come from the applicant's *Summary of safety* in which the following pooling of studies was applied.



Summary of the pooled safety populations

3.3.7.1. Patient exposure

The RMP states that 1,184 female and 522 male subjects were exposed to any dose of oteseconazole in clinical studies. Out of 1,184 female subjects (see table), 928 received multiple doses and 916/928 were exposed to at least 150 mg QD for short periods. Of these, 746 had RVVC.

Table 2.7.4-4 Exposure to oteseconazole in study pools

Study pools	Mean number of days on OTE [a]	Mean total cumulative dose of OTE (mg)	Mean person-year of exposure [b]
Phase I HV pool			
Single dose (n=110)	1.0	210.3	-
Multiple dose (n=75)	11.3	4401.9	-
Phase II non-RVVC pool (n=290)	85.3	9712.1	0.233
Phase II/III RVVC pool (n=746)	86.3	3056.1	0.236

Abbreviations: HV=healthy volunteer; OTE=oteseconazole; RVVC=recurrent vulvovaginal candidiasis

a. Days on OTE were the number of days from date of the first dose of OTE to the date of the last dose of OTE for the study as recorded on the corresponding eCRF or imputed based on the last date a subject received OTE in the study.

b. Person-year of exposure was defined as the days on OTE divided by 365.25.

3.3.7.2. Adverse events

The table below summarises the safety profile for subgroups of the Phase 2/3 pooled population defined by dose regimen. Note that the 1050 mg loading dose column includes those given 150 mg QD for 7 days in Phase 2 or 3. There is a separate column for those who received 1050 mg as the loading dose in CL-017, delivered as 600 mg and 450 mg on days 1 and 2. The 2100 mg loading dose column refers to the 300 mg QD for 7 days regimen tested only in CL-006. The comparison between oteseconazole regimens and placebo is made with a pooled placebo group.

Table 2.7.4-15 Overall summary of AEs – Phase II/III RVVC studies pool

	Oteseconazole							Placebo N=336 n (%)
	150 mg for 12 weeks N=475 n (%)	1050 mg loading dose N=663 n (%)	1050 mg loading dose (Phase III studies) N=580 n (%)	600 mg on Day 1 and 450 mg on Day 2 N=146 n (%)	2100 mg loading dose N=83 n (%)	For 24 weeks N=83 n (%)	Total N=746 n (%)	
Subjects who had any:								
AE	267 (56.2)	377 (56.9)	320 (55.2)	79 (54.1)	58 (69.9)	59 (71.1)	435 (58.3)	207 (61.6)
AE with onset time on or prior to last dose date	164 (34.5)	236 (35.6)	191 (32.9)	45 (30.8)	40 (48.2)	48 (57.8)	276 (37.0)	143 (42.6)
AE with onset time after last dose date	206 (43.4)	284 (42.8)	251 (43.3)	64 (43.8)	41 (49.4)	30 (36.1)	325 (43.6)	148 (44.0)
IMP-related AE	23 (4.8)	36 (5.4)	29 (5.0)	8 (5.5)	9 (10.8)	9 (10.8)	45 (6.0)	22 (6.5)
Severe AE	19 (4.0)	25 (3.8)	22 (3.8)	5 (3.4)	5 (6.0)	3 (3.6)	30 (4.0)	9 (2.7)
SAE	11 (2.3)	14 (2.1)	13 (2.2)	3 (2.1)	3 (3.6)	2 (2.4)	17 (2.3)	10 (3.0)
Fatal AE	0	1 (0.2)	1 (0.2)	1 (0.7)	0	0	1 (0.1)	0
AE leading to interruption of IMP	3 (0.6)	3 (0.5)	1 (0.2)	0	0	0	3 (0.4)	3 (0.9)
AE leading to permanent discontinuation of IMP	4 (0.8)	5 (0.8)	4 (0.7)	1 (0.7)	1 (1.2)	0	6 (0.8)	1 (0.3)

The most frequently reported AEs were reported in similar percentages in the total oteseconazole and pooled placebo groups and across the oteseconazole treatment groups. The SOC Infections and Infestations had the highest percentages of AEs, followed by Reproductive System and Breast Disorders, reflecting very common events in the type of subjects enrolled.

Table 2.7.4-18 AEs observed in at least 5% of subjects by treatment group and Preferred Term – Phase II/III RVVC studies pool

Preferred Term	Oteseconazole							Placebo N=336 n (%)
	150 mg for 12 weeks N=475 n (%)	1050 mg loading dose N=663 n (%)	1050 mg loading dose (Phase III studies) N=580 n (%)	600 mg on Day 1 and 450 mg on Day 2 N=146 n (%)	2100 mg loading dose N=83 n (%)	For 24 weeks N=83 n (%)	Total N=746 n (%)	
Any AE	146 (30.7)	207 (31.2)	173 (29.8)	43 (29.5)	35 (42.2)	32 (38.6)	242 (32.4)	117 (34.8)
Bacterial Vaginosis	35 (7.4)	57 (8.6)	44 (7.6)	16 (11.0)	8 (9.6)	7 (8.4)	65 (8.7)	37 (11.0)
Urinary Tract Infection	28 (5.9)	50 (7.5)	42 (7.2)	18 (12.3)	13 (5.7)	11 (13.3)	63 (8.4)	33 (9.8)
Headache	31 (6.5)	39 (5.9)	34 (5.9)	8 (5.5)	4 (4.8)	2 (2.4)	43 (5.8)	26 (7.7)
Nasopharyngitis	37 (7.8)	42 (6.3)	40 (6.9)	3 (2.1)	7 (8.4)	5 (6.0)	49 (6.6)	15 (4.5)
Sinusitis	22 (4.6)	30 (4.5)	19 (3.3)	2 (1.4)	5 (6.0)	8 (9.6)	35 (4.7)	11 (3.3)
Upper Respiratory Tract Infection	14 (2.9)	24 (3.6)	18 (3.1)	7 (4.8)	3 (3.6)	4 (4.8)	27 (3.6)	18 (5.4)
Nausea	16 (3.4)	26 (3.9)	21 (3.6)	7 (4.8)	4 (4.8)	5 (6.0)	30 (4.0)	8 (2.4)
Arthralgia	5 (1.1)	6 (0.9)	5 (0.9)	1 (0.7)	5 (6.0)	2 (2.4)	11 (1.5)	2 (0.6)

The majority of AEs was of mild or moderate severity, with <1% considered severe and <1% life-threatening when using the final recommended dose regimen.

Table 2.7.4-21 AEs observed in at least 5% of subjects by treatment group, System Organ Class, Preferred Term and maximum severity – incidence rate per 100 person-years, Phase II/III RVVC studies pool

System Organ Class Preferred Term Maximum severity	Oteseconazole														Placebo N=336	
	150 mg for 12 weeks N=475		1050 mg loading dose N=663		1050 mg loading dose (Phase III studies) N=580		600 mg on Day 1 and 450 mg on Day 2 N=146		2100 mg loading dose N=83		For 24 weeks N=83		Total N=746			
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Any AE	267 (56.2)	814.2	377 (56.9)	784.3	320 (55.2)	807.1	79 (54.1)	856.0	58 (69.9)	652.0	59 (71.1)	482.5	435 (58.3)	764.5	207 (61.6)	786.9
Mild	136 (28.6)	552.1	184 (27.8)	498.6	161 (27.8)	516.3	36 (24.7)	445.7	26 (31.3)	360.1	26 (31.3)	254.4	210 (28.2)	477.9	97 (28.9)	481.0
Moderate	112 (23.6)	239.9	168 (25.3)	262.3	137 (23.6)	265.5	38 (26.0)	371.4	27 (32.5)	242.6	30 (36.1)	195.9	195 (26.1)	259.4	101 (30.1)	288.3
Severe	18 (3.8)	21.2	22 (3.3)	18.7	19 (3.3)	19.5	3 (2.1)	17.7	5 (6.0)	49.3	3 (3.6)	32.1	27 (3.6)	23.3	9 (2.7)	17.6
Life-threatening	1 (0.2)	1.0	2 (0.3)	4.0	2 (0.3)	4.9	1 (0.7)	17.7	0	0	0	0	2 (0.3)	3.4	0	0
Death	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	0	0	0	0	1 (0.1)	0.6	0	0

In CL-017 one of the 5 severe AEs in the oteseconazole was considered to be drug related, this being the episode of allergic dermatitis described further below. Of the 5 life-threatening TEAEs reported in the oteseconazole group, four occurred in one subject (cerebrovascular accident, retroperitoneal haemorrhage, deep vein thrombosis and pulmonary embolism) and one case of COVID-19 pneumonia was fatal but these AEs were not considered drug-related.

In CL-011, the single life-threatening TEAE reported in the oteseconazole group was limb amputation following a road traffic accident. The other 7 severe TEAEs reported in the oteseconazole group were considered unrelated to treatment.

In CL-012, the 11 severe TEAEs reported in 10 subjects in the oteseconazole group were not considered to be drug-related.

The percentages reporting AEs considered to be drug-related were low and broadly similar between the groups that received the proposed dose regimen and the pooled placebo group. Rates were slightly higher for the high dose regimen that was tested in study CL-006, based on 83 subjects. The most frequently drug-related AEs were nausea and headache.

As shown below, there were small numbers of subjects considered to have had drug-related abnormalities in liver function tests and ADRs that could have represented drug hypersensitivity. These ADRs are discussed further in following subsections.

Table 2.7.4-23 IMP-related AEs by System Organ Class and Preferred Term, incidence rates per 100 person-years– Phase II/III RVVC studies pool

System Organ Class Preferred Term	Oteseconazole														Placebo N=336	
	150 mg for 12 weeks N=475		1050 mg loading dose N=663		1050 mg loading dose (Phase III studies) N=580		600 mg on Day 1 and 450 mg on Day 2 N=146		2100 mg loading dose N=83		For 24 weeks N=83		Total N=746			
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Any Related AE	23 (4.8)	35.7	36 (5.4)	35.4	29 (5.0)	36.6	8 (5.5)	38.9	9 (10.8)	49.3	9 (10.8)	32.2	45 (6.0)	37.5	22 (6.5)	49.1
Gastrointestinal Disorders	11 (2.3)	15.4	18 (2.7)	15.4	12 (2.1)	13.0	2 (1.4)	7.1	3 (3.6)	15.2	7 (8.4)	23.4	21 (2.8)	15.3	6 (1.8)	10.1
Nausea	5 (1.1)	6.7	9 (1.4)	7.3	7 (1.2)	7.3	2 (1.4)	7.1	2 (2.4)	7.6	3 (3.6)	8.8	11 (1.5)	7.4	2 (0.6)	2.5
Abdominal Pain	1 (0.2)	1.0	2 (0.3)	1.3	1 (0.2)	0.8	0	0	0	0	1 (1.2)	2.9	2 (0.3)	1.1	1 (0.3)	1.3
Diarrhoea	1 (0.2)	1.0	2 (0.3)	1.3	1 (0.2)	0.8	0	0	1 (1.2)	3.8	2 (2.4)	5.8	3 (0.4)	1.7	0	0
Dyspepsia	3 (0.6)	2.9	3 (0.5)	2.0	3 (0.5)	2.4	0	0	0	0	0	0	3 (0.4)	1.7	0	0
Vomiting	0	0	1 (0.2)	0.7	0	0	0	0	0	0	1 (1.2)	2.9	1 (0.1)	0.6	2 (0.6)	2.5
Abdominal Pain Upper	1 (0.2)	1.0	1 (0.2)	0.7	0	0	0	0	0	0	0	0	1 (0.1)	0.6	1 (0.3)	1.3
Constipation	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	1 (0.3)	1.3
Abdominal Discomfort	1 (0.2)	1.0	1 (0.2)	0.7	0	0	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Abdominal Distention	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Gastritis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3
Gastrooesophageal Reflux Disease	0	0	0	0	0	0	0	0	1 (1.2)	3.8	1 (1.2)	2.9	1 (0.1)	0.6	0	0
Nervous System Disorders	4 (0.8)	3.9	7 (1.1)	5.3	7 (1.2)	6.5	3 (2.1)	14.1	2 (2.4)	11.4	0	0	9 (1.2)	6.2	6 (1.8)	16.4
Headache	3 (0.6)	2.9	5 (0.8)	4.0	5 (0.9)	4.9	2 (1.4)	10.6	2 (2.4)	7.6	0	0	7 (0.9)	4.5	6 (1.8)	16.4
Dizziness	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	1 (1.2)	3.8	0	0	2 (0.3)	1.1	0	0
Parosmia	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Skin and Subcutaneous Tissue Disorders	2 (0.4)	1.9	6 (0.9)	4.0	5 (0.9)	4.1	4 (2.7)	14.1	1 (1.2)	3.8	0	0	7 (0.9)	4.0	3 (0.9)	3.8
Dermatitis Allergic	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	1 (1.2)	3.8	0	0	2 (0.3)	1.1	1 (0.3)	1.3
Rash	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	0	0	0	0	1 (0.1)	0.6	2 (0.6)	2.5
Blister	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0

System Organ Class Preferred Term	Oteseconazole														Placebo N=336	
	150 mg for 12 weeks N=475		1050 mg loading dose N=663		1050 mg loading dose (Phase III studies) N=580		600 mg on Day 1 and 450 mg on Day 2 N=146		2100 mg loading dose N=83		For 24 weeks N=83		Total N=746			
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Dermatitis Contact	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	0	0	0	0	1 (0.1)	0.6	0	0
Seborrhoeic Dermatitis	1 (0.2)	1.0	1 (0.2)	0.7	0	0	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Urticaria	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	0	0	0	0	1 (0.1)	0.6	0	0
Infections and Infestations	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	1 (1.2)	7.6	1 (1.2)	5.8	2 (0.3)	1.7	5 (1.5)	10.1
Vulvovaginal Candidiasis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3 (0.9)	5.0
Vulvovaginal Mycotic Infection	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	1 (0.3)	1.3
Bacterial Vaginosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	3.8
Nasopharyngitis	0	0	0	0	0	0	0	0	1 (1.2)	3.8	1 (1.2)	2.9	1 (0.1)	0.6	0	0
Sinusitis	0	0	0	0	0	0	0	0	1 (1.2)	3.8	1 (1.2)	2.9	1 (0.1)	0.6	0	0
Reproductive System and Breast Disorders	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	1 (1.2)	3.8	0	0	2 (0.3)	1.1	3 (0.9)	3.8
Vulvovaginal Pruritus	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2 (0.6)	2.5
Menorrhagia	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Vaginal Discharge	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3
Vulvovaginal Dryness	0	0	0	0	0	0	0	0	1 (1.2)	3.8	0	0	1 (0.1)	0.6	0	0
Investigations	2 (0.4)	2.9	3 (0.5)	2.7	3 (0.5)	3.3	1 (0.7)	3.5	0	0	0	0	3 (0.4)	2.3	1 (0.3)	1.3
Blood Creatine Phosphokinase Increased	1 (0.2)	1.0	2 (0.3)	1.3	2 (0.3)	1.6	1 (0.7)	3.5	0	0	0	0	2 (0.3)	1.1	1 (0.3)	1.3
Alanine Aminotransferase Increased	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Aspartate Aminotransferase Increased	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Blood and Lymphatic System Disorders	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	1 (0.3)	1.3
Neutropenia	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	1 (0.3)	1.3
General Disorders and Administration Site Conditions	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	1 (1.2)	3.8	0	0	2 (0.3)	1.1	0	0

System Organ Class Preferred Term	Oteseconazole														Placebo N=336	
	150 mg for 12 weeks N=475		1050 mg loading dose N=663		1050 mg loading dose (Phase III studies) N=580		600 mg on Day 1 and 450 mg on Day 2 N=146		2100 mg loading dose N=83		For 24 weeks N=83		Total N=746			
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Fatigue	0	0	0	0	0	0	0	0	1 (1.2)	3.8	0	0	1 (0.1)	0.6	0	0
Feeling Jittery	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Musculoskeletal and Connective Tissue Disorders	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	1 (1.2)	3.8	1 (1.2)	2.9	2 (0.3)	1.1	0	0
Muscle Spasms	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Myalgia	0	0	0	0	0	0	0	0	1 (1.2)	3.8	1 (1.2)	2.9	1 (0.1)	0.6	0	0
Vascular Disorders	2 (0.4)	1.9	2 (0.3)	1.3	2 (0.3)	1.6	0	0	0	0	0	0	2 (0.3)	1.1	0	0
Hot Flush	2 (0.4)	1.9	2 (0.3)	1.3	2 (0.3)	1.6	0	0	0	0	0	0	2 (0.3)	1.1	0	0
Ear and Labyrinth Disorders	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3
Ear Pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3
Hepatobiliary Disorders	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Biliary Colic	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Immune System Disorders	1 (0.2)	3.9	1 (0.2)	2.7	1 (0.2)	3.3	0	0	0	0	0	0	1 (0.1)	2.3	0	0
Drug Hypersensitivity	1 (0.2)	3.9	1 (0.2)	2.7	1 (0.2)	3.3	0	0	0	0	0	0	1 (0.1)	2.3	0	0
Psychiatric Disorders	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3
Nervousness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3

Abbreviations: IMP=investigational medicinal product; IR=incidence rate; RVVC=recurrent vulvovaginal candidiasis; AE= adverse event
Note: AEs were coded using MedDRA (Version 21).
Note: any AEs noted as 'possibly related,' 'probably related,' or 'definitely related' were considered as IMP-related adverse events. Any AEs with missing relationship were counted as IMP-related.
Note: person-years of exposure was defined as the days on IMP divided by 365.25. The incidence per 100 person-years of exposure was calculated as the total number of AEs of a given type experienced in a given treatment group divided by the sum of the per person-year exposure for the treatment group, multiplied by 100.

AEs of special interest (AESIs)

Liver disorder-related events reported as AEs

Liver-related events reported as AEs were uncommon, occurring in 1 subject (6.3%) in the placebo group and 1 (0.9%) in the total oteseconazole group in the Phase I single dose pool, 1 (0.3%) in the total oteseconazole group in the Phase 2 non-RVVC studies pool and 7 (0.9%) in the total oteseconazole group in the Phase 2/3 RVVC studies pool. In the Phase 2/3 RVVC studies pool, the only individual PT reported for >1 subject was AST increased (3 subjects [0.4%]) and ALT increased (2 subjects [0.3%]). All events of AST increased were mild in severity and 1 was considered drug-related. All events of ALT increased were mild or moderate in severity and 1 was considered drug-related. These elevations were transient and there were no AEs of cholestasis or fulminant hepatic failure. The AE of hepatitis (sub-hepatic inflammation after laparoscopic intervention) was moderate in severity, considered unrelated and had resolved by the time of reporting.

Table 2.7.4-32 Liver-related AEs by studies pools

Preferred Term	Study pools							
	Phase I HV single dose		Phase I HV multiple dose		Phase II non-RVVC		Phase II/III RVVC	
	Placebo N=16 n (%)	OTE N=110 n (%)	Placebo N=8 n (%)	OTE N=75 n (%)	Placebo N=59 n (%)	OTE N=290 n (%)	Placebo N=336 n (%)	OTE N=746 n (%)
Any liver-related AE	1 (6.3)	1 (0.9)	0	0	0	1 (0.3)	0	7 (0.9)
Aspartate Aminotransferase Increased	0	0	0	0	0	0	0	3 (0.4)
Alanine Aminotransferase Increased	1 (6.3)	1 (0.9)	0	0	0	0	0	2 (0.3)
Liver Function Test Increased	0	0	0	0	0	1 (0.3)	0	0
Hepatic Enzyme Increased	0	0	0	0	0	0	0	1 (0.1)
Hepatic Steatosis	0	0	0	0	0	0	0	1 (0.1)
Hepatitis	0	0	0	0	0	0	0	1 (0.1)
Transaminases Increased	0	0	0	0	0	0	0	1 (0.1)

Abbreviations: HV=healthy volunteer; OTE=oteseconazole; RVVC=recurrent vulvovaginal candidiasis
Note: AEs were coded using MedDRA (Version 21).
Note: liver-related AEs consisted of the broad and narrow terms in each of the following individual SMQs: Cholestasis and jaundice of hepatic origin (SMQ); Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ); Hepatitis, non-infectious (SMQ); Liver neoplasms, benign (incl cysts and polyps) (SMQ); Liver malignant tumours (SMQ); Liver tumours of unspecified malignancy (SMQ); Liver related investigations, signs and symptoms (SMQ); and Liver related coagulation and bleeding disturbances (SMQ).

The table below shows numbers with specified magnitudes of increases in liver function tests in the Phase 2/3 RVVC studies pool.

Two subjects experienced ALT increase of >5xULN:

In CL-012, a 52-year old regular alcohol user since 20 years completed her week 12 last weekly dose of oteseconazole 150 mg on 8 May 2019. ALT, AST, bilirubin, CK and ALP were always within normal ranges except ALT and AST starting from week 24 when ALT was 1.4xULN and AST was just above ULN. At week 30, ALT was 1.7xULN and AST 1.3xULN, increasing to 5.97xULN and AST 4.6xULN. By week 36, ALT was 1.9xULN and AST 1.1xULN and by week 42), ALT was 1.5xULN and AST just above ULN. The investigator assessed the elevated transaminases as unrelated to the IMP.

In CL-006, a 26-year old with AST of 2.3xULN at baseline was exposed to oteseconazole 300 mg dose for 24 weeks. At day 7, AST was 1.7xULN, ALT 2.3xULN and ALP was just above ULN. At week 4, ALT increased to 7.9xULN, AST 4.5xULN and ALP 1.2xULN. Eight days later treatment was interrupted due to liver test results for two weeks and at that time ALT was 3.3xULN and AST 1.7xULN. At week 8, ALT was 2.1xULN, AST 1.9xULN and ALP was just above ULN. At week 12, ALT was 2.3xULN, AST 2.0xULN and ALP 1.1xULN. At week 18, ALT decreased to 1.3xULN, AST 1.1xULN and from week 24 all relevant laboratory results were WNL.

Four subjects had AST increases of >5xULN, two in CL-006 and two in CL-017.

One subject had normal values except at week 8 (3.3xULN) and one week later (unscheduled visit: 2.2xULN). Treatment was continued. Another had AST WNL except for week 36 2.5xULN and one week later 5.3xULN and a further subject had AST WNL except at week 36 (1.1xULN) and one week later (2.6xULN). The fourth subject had an isolated increase in AST and ALT at week 50 (5.6xULN and 2.8xULN) that was associated with a CK increase to 39.1xULN.

Table 2.7.4-33 Liver-related abnormal laboratory parameters by times of ULN– Phase II/III RVVC studies pool

Laboratory parameter	Oteseconazole							Placebo N=336
	150 mg for 12 weeks N=475	1050 mg loading dose N=663	1050 mg loading dose (Phase III studies) N=580	600 mg on Day 1 and 450 mg on Day 2 N=146	2100 mg loading dose N=83	For 24 weeks N=83	Total OTE N=746	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
ALT								
> 1.5 x ULN	23/468 (4.9%)	28/652 (4.3%)	27/569 (4.7%)	4/142 (2.8%)	5/81 (6.2%)	3/82 (3.7%)	33/733 (4.5%)	16/328 (4.9%)
> 3 x ULN	2/468 (0.4%)	3/652 (0.5%)	3/569 (0.5%)	1/142 (0.7%)	2/81 (2.5%)	1/82 (1.2%)	5/733 (0.7%)	2/328 (0.6%)
> 5 x ULN	1/468 (0.2%)	1/652 (0.2%)	1/569 (0.2%)	0/142	1/81 (1.2%)	0/82	2/733 (0.3%)	0/328
> 10 x ULN	0/468	0/652	0/569	0/142	0/81	0/82	0/733	0/328
AST								
> 1.5 x ULN	24/468 (5.1%)	30/652 (4.6%)	27/569 (4.7%)	6/142 (4.2%)	8/81 (9.9%)	4/82 (4.9%)	38/733 (5.2%)	17/328 (5.2%)
> 3 x ULN	4/468 (0.9%)	6/652 (0.9%)	6/569 (1.1%)	2/142 (1.4%)	3/81 (3.7%)	1/82 (1.2%)	9/733 (1.2%)	1/328 (0.3%)
> 5 x ULN	0/468	2/652 (0.3%)	2/569 (0.4%)	2/142 (1.4%)	2/81 (2.5%)	1/82 (1.2%)	4/733 (0.5%)	0/328
> 10 x ULN	0/468	0/652	0/569	0/142	1/81 (1.2%)	1/82 (1.2%)	1/733 (0.1%)	0/328
Total bilirubin								
> 1.5 x ULN	6/468 (1.3%)	6/652 (0.9%)	6/569 (1.1%)	0/142	1/81 (1.2%)	0/82	7/733 (1.0%)	3/328 (0.9%)
> 2 x ULN	0/468	0/652	0/569	0/142	0/81	0/82	0/733	2/328 (0.6%)
Alkaline phosphatase								
> 1.5 x ULN	5/468 (1.1%)	6/652 (0.9%)	3/569 (0.5%)	1/142 (0.7%)	0/81	0/82	6/733 (0.8%)	4/328 (1.2%)

Abbreviations: ULN=upper limit of normal; OTE=oteseconazole; RVVC=recurrent vulvovaginal candidiasis; ALT=alanine aminotransferase, AST=aspartate aminotransferase
Note: the denominators are the number of subjects with non-missing lab result for the lab test and treatment group.

Nervous system and ocular events

Nervous system events were common and were reported for similar proportions across treatment groups. In the Phase 2/3 pool, the most frequently reported PT was headache (7.7% in the placebo group and 5.8% in the total oteseconazole group), but only one event was severe and most were considered not drug-related to IMP. Dysgeusia was reported more commonly with oteseconazole but only at the highest loading dose. Treatment-emergent eye disorder events in adult female study subjects did not point to a particular risk for oteseconazole and none of the AEs was considered treatment-related.

Pregnancies

In the Phase 2/3 RVVC pool, information is available for 34 pregnancies reported for 29 subjects of which 20 received oteseconazole. Pregnancy outcomes are shown below for 23 pregnancies.

Table 2.7.4-41 Summary of pregnancies in Phase II/III RVVC studies pool

	Oteseconazole							Placebo N=336 n (%)
	150 mg for 12 weeks N=475 n (%)	1050 mg loading dose N=663 n (%)	1050 mg loading dose (Phase III studies) N=580 n (%)	600 mg on Day 1 and 450 mg on Day 2 N=146 n (%)	2100 mg loading dose N=83 n (%)	For 24 weeks N=83 n (%)	Total N=746 n (%)	
Pregnancy	12 (2.5)	17 (2.6)	11 (1.9)	3 (2.1)	3 (3.6)	3 (3.6)	20 (2.7)	9 (2.7)

Table 2.7.4-42 Listing of pregnancies in Phase II/III RVVC studies pool

Study	OTE or placebo	Estimated onset date [a]	Estimated due date	Outcome	First IMP dose date	Last IMP dose date
CL-011	Placebo	07 Jan 2019	21 Aug 2019	Healthy, live birth	16 Oct 2018	07 Jan 2019
CL-011	OTE	03 Aug 2019	07 Apr 2020	Healthy, live birth	22 Mar 2019	12 Jun 2019
CL-011	OTE	24 Aug 2019	25 Mar 2020	Healthy, live birth; C-section	07 May 2019	30 Jul 2019
CL-011	Placebo	31 Aug 2019	06 Jun 2020	Not reported	18 Jun 2019	10 Sep 2019
CL-012	OTE	31 Oct 2019	01 Jun 2020	Not reported	17 Sep 2019	28 Oct 2019
CL-012	Placebo	17 Dec 2019	21 Aug 2020	Healthy, live birth	05 Nov 2019	10 Dec 2019
CL-012	OTE	05 Jan 2020	13 Oct 2020	Healthy, live birth	29 May 2019	22 Aug 2019
CL-012	OTE	06 Mar 2020	26 Nov 2020	Healthy, live birth; C-section	09 Oct 2019	31 Dec 2019
CL-012	Placebo	28 Apr 2020	19 Jan 2021	Healthy, live birth; C-section	15 Jul 2019	21 Jul 2019
CL-012	Placebo	05 Jun 2020	08 Mar 2021	Elective termination	25 Jun 2019	16 Sep 2019
CL-012	OTE	15 May 2020	28 Jan 2021	Healthy, live birth	11 Oct 2019	01 Jan 2020
CL-012	OTE	09 Jul 2020	13 Mar 2021	Healthy, live birth	31 Jul 2019	23 Oct 2019
CL-012	OTE	14 Sep 2020	04 May 2021	Elective termination	18 Sep 2019	25 Dec 2019
CL-017	OTE	07 Oct 2019	12 Jul 2020	Elective termination	12 Jun 2019	04 Sep 2019
CL-017	OTE	06 May 2020	12 Dec 2020	Elective termination	12 Jun 2019	04 Sep 2019
CL-017	OTE	19 Nov 2019	30 Jul 2020	Spontaneous abortion	14 Aug 2019	06 Nov 2019
CL-017	OTE	07 Apr 2020	13 Dec 2020	Healthy, live birth; C-section	14 Aug 2019	06 Nov 2019
CL-017	Placebo	20 May 2020	31 Dec 2020	Healthy, live birth; C-section	16 Sep 2019	09 Dec 2019
CL-017	OTE	07 Jul 2020	04 Mar 2021	Healthy, live birth	15 Oct 2019	07 Jan 2020
CL-017	OTE	-	13 Feb 2021	Healthy, live birth	15 Oct 2019	07 Jan 2020
CL-006	OTE	18 Jul 2015	-	Elective termination	8 May 2015	29 Oct 2015
CL-006	OTE	03 Feb 2016	-	Elective termination	12 Nov 2015	04 May 2016
CL-006	OTE	10 May 2016	-	Healthy, live birth	12 Nov 2015	04 May 2016
CL-006	OTE	03 Mar 2016	-	Elective termination	15 Apr 2015	29 Sep 2015
CL-006	OTE	4 May 2016	-	Healthy, live birth	12 Oct 2015	27 Mar 2016
CL-006	OTE	07 Aug 2015	-	Healthy, live birth	26 Jun 2015	31 Jul 2015
CL-006	OTE	20 Aug 2016	-	Spontaneous abortion	22 Sep 2015	07 Mar 2016
CL-006	OTE	02 Apr 2015	-	Healthy, live birth	12 Mar 2015	26 Mar 2015
CL-006	OTE	-	-	Miscarriage in Feb 2020	12 Mar 2015	26 Mar 2015
CL-006	OTE	29 Jan 2016	-	Elective termination	10 Dec 2015	25 May 2016
CL-006	OTE	19 Aug 2015	-	Chemical pregnancy	24 Jun 2015	18 Aug 2015
CL-006	Placebo	24 Aug 2015	-	Chemical pregnancy	15 Jun 2015	19 Aug 2015
CL-006	Placebo	15 Feb 2016	-	Healthy, live birth	08 May 2015	17 Sep 2015
CL-006	Placebo	-	-	Healthy, live birth	02 Dec 2015	17 May 2016

Abbreviations: IMP=investigational medicinal product; OTE=oteseconazole; RVVC=recurrent vulvovaginal candidiasis
a. Date of positive pregnancy test or start of last menstrual period.

In oteseconazole-treated subjects there were 13 healthy live births (including 3 C-section deliveries and 1 which was premature at 32 weeks of gestation), 7 elective terminations (including 2 in one

subject and a termination due to foetal valvular defect and pulmonary stenosis, 2 spontaneous miscarriages or abortions and one chemical pregnancy (failed to implant after 8 weeks of treatment in CL-006). In CL-012, 2 subjects were lost to follow-up and the pregnancy outcomes were not reported. The percentages of miscarriages in the oteseconazole groups were similar to reported background rates (Ventura 2012).

In the Phase 2 non-RVVC studies pool there were no pregnancies in the oteseconazole dose groups. One pregnancy was reported in the Phase I HV multiple dose studies pool in the ≥ 300 mg oteseconazole dose group in CL-008. This subject was noncompliant with her method of contraception. The pregnancy was electively terminated.

3.3.7.3. *Serious adverse events, deaths, and other significant events*

The single death in the programme occurred in CL-017. As mentioned above, this was due to COVID-19 pneumonia in a subject in the oteseconazole group.

- In CL-017, there were 8 SAEs in 3 subjects (2%) in the oteseconazole group (appendicitis, pneumonia viral, acute respiratory failure [due to COVID-19 pneumonia], pulmonary embolism, anaemia, retroperitoneal haemorrhage, cerebrovascular accident and deep vein thrombosis) and one SAE occurred in 1 subject (1%) in the fluconazole/placebo group (pneumonia). None was considered related to IP by the investigator.
- In CL-011, 6 subjects had 12 SAEs, including 3 subjects in the oteseconazole group with SAEs of postoperative wound infection, tubo-ovarian abscess, endometriosis and limb amputation. None of the SAEs was considered treatment-related by the investigators.
- In CL-012, 7 subjects (3%) in the oteseconazole group and 5 (5%) in the placebo group had SAEs. No serious TEAE was reported in >1 subject and none was considered to be treatment-related by the investigators.

There were no SAEs reported in the Phase 1 studies or in CL-003 or -004. In CL-005, none of the SAEs was considered drug-related by investigators and all seem to have been related to pre-existing or new onset underlying medical conditions.

3.3.7.4. Laboratory findings

CL-017
Abnormal results haematological results were reported in ≥10% of subjects in both treatment groups for multiple parameters but no changes were considered clinically relevant.

In the oteseconazole and comparator groups, glucose was abnormal in ≥10% of subjects at several time points likely due to the collection of non-fasting blood samples and the inclusion of subjects with controlled diabetes mellitus (HbA1c <8.5% at Screening).
Other abnormal clinical chemistry results were reported in ≥10% of subjects in both treatment groups for multiple parameters but these were not considered clinically relevant. The rates for any treatment-emergent graded laboratory toxicity were generally comparable between groups except for glucose, with a graded abnormality reported for 58 subjects (41%) in the oteseconazole group and 19 subjects (28%) in the fluconazole/placebo group. Single subjects in the oteseconazole group and none in the comparator group had shifts from Grade 0 at baseline to Grade 3 (worst overall) for ALT, AST, CK and neutrophils. Shifts from Grade 0 at baseline to Grade 4 (worst overall) were observed for AST (one oteseconazole), CK (3 oteseconazole) and neutrophils (one oteseconazole). No subject had treatment-emergent abnormal hepatic laboratory values that met potential Hy's Law criteria.

CL-011 and CL-012

Graded haematological abnormalities occurred at similar or lower rates in the oteseconazole group. Rates for any graded abnormal chemistry result and for shifts from Grade 0 at baseline to Grade 3 or 4 were generally similar between groups.

3.3.7.5. Safety in special populations

Age

Due to the indication and target population, there are almost no data in subjects aged <16 years (2 oteseconazole and one placebo) or aged >65 years (3 and 2, respectively). For the most commonly reported AEs, there were no major differences in reporting rates for the three largest age sub-populations. Within the largest age sub-groups there were no major differences between oteseconazole and placebo for proportions of AEs that were categorised as severe or serious or were considered related to treatment.

Table 2.7.4-54 AEs observed in at least 5% of subjects in a treatment group by Preferred Term, by age group in Phase II/III RVVC studies pool

Preferred term	Age group									
	12 to 17 y		18 to 25 y		18 to 44 y		45 to 65 y		>65 y	
	OTE N=2 n (%)	Placebo N=1 n (%)	OTE N=167 n (%)	Placebo N=71 n (%)	OTE N=618 n (%)	Placebo N=276 n (%)	OTE N=123 n (%)	Placebo N=57 n (%)	OTE N=3 n (%)	Placebo N=2 n (%)
Any AE	0	1 (100.0)	97 (58.1)	44 (62.0)	357 (57.8)	167 (60.5)	76 (61.8)	37 (64.9)	2 (66.7)	2 (100.0)
Bacterial Vaginosis	0	0	17 (10.2)	10 (14.1)	58 (9.4)	29 (10.5)	7 (5.7)	8 (14.0)	0	0
Urinary Tract Infection	0	0	19 (11.4)	10 (14.1)	51 (8.3)	25 (9.1)	11 (8.9)	7 (12.3)	1 (33.3)	1 (50.0)
Headache	0	0	10 (6.0)	6 (8.5)	30 (4.9)	21 (7.6)	13 (10.6)	5 (8.8)	0	0
Nasopharyngitis	0	0	15 (9.0)	4 (5.6)	42 (6.8)	13 (4.7)	7 (5.7)	2 (3.5)	0	0
Sinusitis	0	0	7 (4.2)	3 (4.2)	29 (4.7)	9 (3.3)	6 (4.9)	2 (3.5)	0	0
Upper Respiratory Tract Infection	0	0	4 (2.4)	8 (11.3)	23 (3.7)	18 (6.5)	4 (3.3)	0	0	0
Nausea	0	0	9 (5.4)	2 (2.8)	26 (4.2)	6 (2.2)	3 (2.4)	2 (3.5)	1 (33.3)	0
Arthralgia	0	0	2 (1.2)	0	9 (1.5)	2 (0.7)	2 (1.6)	0	0	0

Race

The highest AE reporting rates were in Asians (mostly Japanese) but there were no marked differences between oteseconazole and placebo within the defined racial groups that raise concerns regarding oteseconazole.

Table 2.7.4-61 AEs observed in at least 5% of subjects in a treatment group by Preferred Term by race and ethnicity in Phase II/III RVVC studies pool

Preferred Term	Race								Ethnicity			
	White		Black or African American		Asian		Other		Hispanic		Non-Hispanic	
	OTE N=529 n (%)	Placebo N=242 n (%)	OTE N=162 n (%)	Placebo N=72 n (%)	OTE N=40 n (%)	Placebo N=17 n (%)	OTE N=14 n (%)	Placebo N=5 n (%)	OTE N=114 n (%)	Placebo N=54 n (%)	OTE N=630 n (%)	Placebo N=282 n (%)
Any AE	286 (54.1)	142 (58.7)	107 (66.0)	47 (65.3)	34 (85.0)	15 (88.2)	7 (50.0)	3 (60.0)	66 (57.9)	30 (55.6)	367 (58.3)	177 (62.8)
Bacterial Vaginosis	30 (5.7)	18 (7.4)	31 (19.1)	16 (22.2)	3 (7.5)	1 (5.9)	0	2 (40.0)	8 (7.0)	11 (20.4)	57 (9.0)	26 (9.2)
Urinary Tract Infection	43 (8.1)	19 (7.9)	19 (11.7)	10 (13.9)	1 (2.5)	2 (11.8)	0	2 (40.0)	7 (6.1)	5 (9.3)	56 (8.9)	28 (9.9)
Headache	28 (5.3)	18 (7.4)	14 (8.6)	6 (8.3)	1 (2.5)	2 (11.8)	0	0	8 (7.0)	4 (7.4)	35 (5.6)	22 (7.8)
Nasopharyngitis	26 (4.9)	11 (4.5)	5 (3.1)	0	17 (42.5)	4 (23.5)	1 (7.1)	0	13 (11.4)	0	36 (5.7)	15 (5.3)
Sinusitis	28 (5.3)	8 (3.3)	6 (3.7)	2 (2.8)	1 (2.5)	1 (5.9)	0	0	6 (5.3)	2 (3.7)	29 (4.6)	9 (3.2)
Upper Respiratory Tract Infection	20 (3.8)	13 (5.4)	5 (3.1)	4 (5.6)	1 (2.5)	1 (5.9)	1 (7.1)	0	2 (1.8)	3 (5.6)	25 (4.0)	15 (5.3)
Nausea	17 (3.2)	5 (2.1)	11 (6.8)	1 (1.4)	1 (2.5)	1 (5.9)	1 (7.1)	1 (20.0)	5 (4.4)	0	25 (4.0)	8 (2.8)
Arthralgia	6 (1.1)	2 (0.8)	3 (1.9)	0	2 (5.0)	0	0	0	1 (0.9)	0	10 (1.6)	2 (0.7)

3.3.7.6. Immunological events

Thus far, anaphylaxis has not been reported.

In CL-017 dermatitis allergic, dermatitis contact, rash and urticaria were considered treatment-related by the investigator although none was serious. One case of dermatitis allergic resulted in discontinuation of oteseconazole (see below).

In CL-011, none of the skin rashes or cases of urticaria (4 oteseconazole [2%] and one comparator [<1%]) were considered related to oteseconazole by investigators.

In CL-012, the single report of rash in the oteseconazole group was not considered treatment-related by the investigator.

Hypersensitivity and skin and subcutaneous rash-related AEs were common and were reported for similar proportions across oteseconazole and placebo groups. In Phase 2/3 studies, the most frequently reported PT was rash, in 4 (1.2%) in the placebo group and 10 (1.3%) in the total oteseconazole group. All events of rash were mild in severity except for one moderate event and most were not considered to be drug-related.

Two subjects had AEs of drug hypersensitivity and one had an event of hypersensitivity. Both events were ascribed to other concomitant medications.

- In CL-012, one subject had 4 events of drug hypersensitivity that were attributed to allergy to nitrofurantoin and to ibuprofen.
- In CL-005, one subject in each group had an event of hypersensitivity that was moderate in severity and considered not treatment-related.

Table 2.7.4-35 Hypersensitivity and skin and subcutaneous rash-related AEs by studies pools

Preferred Term	Study pool							
	Phase I HV single dose		Phase I HV multiple dose		Phase II non-RVVC		Phase II/III RVVC	
	Placebo N=16 n (%)	OTE N=110 n (%)	Placebo N=8 n (%)	OTE N=75 n (%)	Placebo N=59 n (%)	OTE N=290 n (%)	Placebo N=336 n (%)	OTE N=746 n (%)
Any hypersensitivity and skin and subcutaneous rash-related AE	0	0	0	3 (4.0)	1 (1.7)	8 (2.8)	10 (3.0)	23 (3.1)
Rash	0	0	0	3 (4.0)	0	2 (0.7)	4 (1.2)	10 (1.3)
Dermatitis	0	0	0	0	0	2 (0.7)	1 (0.3)	3 (0.4)
Skin Exfoliation	0	0	0	0	0	2 (0.7)	0	0
Dermatitis Allergic	0	0	0	0	0	1 (0.3)	1 (0.3)	2 (0.3)
Dermatitis Atopic	0	0	0	0	0	1 (0.3)	0	0
Drug Hypersensitivity	0	0	0	0	1 (1.7)	0	0	1 (0.1)
Hypersensitivity	0	0	0	0	0	1 (0.3)	0	0
Urticaria	0	0	0	0	0	1 (0.3)	1 (0.3)	5 (0.7)
Pruritus Generalised	0	0	0	0	0	0	1 (0.3)	1 (0.1)
Drug Eruption	0	0	0	0	0	0	1 (0.3)	0
Rash Generalised	0	0	0	0	0	0	0	1 (0.1)
Rash Vesicular	0	0	0	0	0	0	1 (0.3)	0

Abbreviations: HV=healthy volunteer; OTE=oteseconazole; RVVC=recurrent vulvovaginal candidiasis;
Note: AEs were coded using MedDRA (Version 21).
Note: hypersensitivity and skin and subcutaneous rash-related AEs consisted of selected preferred terms from hypersensitivity (SMQ) and preferred terms for rashes within system organ class of skin and subcutaneous events.

3.3.7.7. Discontinuation due to adverse events

Phase 2/3 RVVC studies

The only AE leading to discontinuation of oteseconazole that was reported for >1 subject in Phase 2 and 3 RVVC studies was dermatitis allergic, with one subject in CL-017 and one subject in CL-006.

The subject in CL-006 had onset on Day 9 and the dermatitis was of moderate severity and non-serious. It was considered drug-related by the investigator and resolved on Day 45.

CL-017 - One subject in the oteseconazole group discontinued IP due to dermatitis allergic with onset on Day 1. The event was severe, not serious, was considered treatment-related by the investigator, led to discontinuation from the study and had resolved by the time of reporting.

CL-011 - One subject in the oteseconazole group discontinued due to a vaginal infection that was non-serious and considered by the investigator to be unrelated to treatment. It seems this was actually an episode of VVC and that the patient withdrew consent so that non-study (and not allowed under the protocol) treatment could be given.

CL-012 - Two subjects (<1%) in the oteseconazole group discontinued treatment due to AEs of abdominal distension and blister. Abdominal distension was moderate in severity, not serious and considered possibly treatment-related by the investigator. The blister was moderate in severity, not serious and considered possibly treatment-related by the investigator.

Table 2.7.4-30 AEs leading to IMP discontinuation by System Organ Class and Preferred Term, incidence rates per 100 person-years – Phase II/III RVVC studies pool

System Organ Class Preferred Term	Oteseconazole														Placebo N=336	
	150 mg for 12 weeks N=475		1050 mg loading dose N=663		1050 mg loading dose (Phase III studies) N=580		600 mg on Day 1 and 450 mg on Day 2 N=146		2100 mg loading dose N=83		For 24 weeks N=83		Total N=746			
	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR	n (%)	IR
Any AE leading to IMP discontinuation	4 (0.8)	3.9	5 (0.8)	3.3	4 (0.7)	3.3	1 (0.7)	3.5	1 (1.2)	3.8	0	0	6 (0.8)	3.4	1 (0.3)	1.3
Skin and Subcutaneous Disorders	1 (0.2)	1.0	2 (0.3)	1.3	2 (0.3)	1.6	1 (0.7)	3.5	1 (1.2)	3.8	0	0	3 (0.4)	1.7	0	0
Dermatitis Allergic	0	0	1 (0.2)	0.7	1 (0.2)	0.8	1 (0.7)	3.5	1 (1.2)	3.8	0	0	2 (0.3)	1.1	0	0
Blister	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Gastrointestinal Disorders	2 (0.4)	1.9	2 (0.3)	1.3	1 (0.2)	0.8	0	0	0	0	0	0	2 (0.3)	1.1	0	0
Abdominal Distention	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Pancreatitis	1 (0.2)	1.0	1 (0.2)	0.7	0	0	0	0	0	0	0	0	1 (0.1)	0.6	0	0
Infections and Infestations	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	1 (0.3)	1.3
Influenza	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1 (0.3)	1.3
Vaginal Infection	1 (0.2)	1.0	1 (0.2)	0.7	1 (0.2)	0.8	0	0	0	0	0	0	1 (0.1)	0.6	0	0

Other studies

One case of rash in the oteseconazole group led to discontinuation in Phase I. This involved a 19-year-old African American male enrolled in CL-008 who developed a rash on the fourth day of dosing at 300 mg/day, which was considered to be possibly dermatographia. The subject discontinued treatment and the rash completely resolved by the following day. The event was considered unlikely drug-related. In the other Phase 2 studies the most frequently reported AEs leading to oteseconazole discontinuation were nausea and dysgeusia, which occurred only in the highest loading dose group (8400 mg).

3.3.7.8. Post marketing experience

There are no post-marketing data included in the MAA. However, the product was approved in the US in April 2022 *to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential*. There is no information on whether the product has been launched in the US.

3.3.8. Discussion on clinical safety

Safety database

The most relevant safety information comes from the Phase 2 (CL-006; in which 2/4 cohorts received 150 mg Q for 7 days as a loading dose and 1/4 cohorts received 150 mg weekly for 12 weeks) and Phase 3 (CL-011, 012 and 017) studies in women with RVVC. The applicant counts 746 women as exposed to oteseconazole in these 4 studies but 663/746 received the 1050 mg loading dose (the other 83 received a 2100 mg loading dose in CL-006).

Of the 663 subjects given a total loading dose of 1050 mg, only CL-017 provides safety data on 146 subjects who received 600 mg on day 1 and 450 mg on day 2.

With a higher Cmax with this 2-dose loading regimen vs. 150 mg QD for 7 days, it is pertinent that the applicant's tables show the safety data separately for these 146 subjects.

Pooling of safety data across placebo groups is acceptable since the selection criteria were comparable between the four studies in women with RVVC.

Duration of exposure and follow-up

For the maintenance regimen of 150 mg weekly commencing 2 weeks after start of the loading regimen, the maximum duration of dosing was 12 weeks in the RVVC studies and the median duration of dosing in Phase 3 studies was ~85 days. The duration of follow-up in these four studies was a maximum of 50 weeks from time of randomisation and 37 weeks after the last dose of oteseconazole.

Safety profile

For the most part, the observed AEs and ADRs with oteseconazole do not suggest major safety concerns associated with the final recommended posology. With the 1050 mg loading dose, administered either as 150 mg QD for 7 days or as 600 mg followed by 450 mg, and with 150 mg once weekly, the overall reporting rates were generally comparable to those for the pooled placebo group. While severe AEs and AEs leading to discontinuation occurred slightly more frequently with oteseconazole vs. placebo, the actual rates were <5% and <1% across groups, respectively.

Leaving aside the AEs concerning the reproductive system and intercurrent genitourinary, or other types of infections, headache and nausea figure prominently among the most common AEs reported. However, while nausea and several other gastrointestinal SOC AEs were slightly more common with oteseconazole, rates for headache were higher with placebo. With the exception of the 300 mg dose groups in CL-006, the total rates for reporting ADRs were comparable between the oteseconazole and placebo groups. The most frequently reported drug-related AEs were nausea and headache.

While the rates for any severe AE were 3.4-4% for those who received oteseconazole 1050 mg loading doses and then 150 mg weekly, the rate for pooled placebo subjects was 2.7%. However, the rates in CL-017 were 2% for oteseconazole and 4% for the fluconazole/placebo group. In Phase 3 studies only one severe AE was considered to be oteseconazole-related, this being a case of allergic dermatitis in CL-017 with onset on day 1 that led to discontinuation of treatment and had resolved by the time of reporting. This was the only discontinuation due to an AE in the study.

In Phase 2/3 RVVC studies there were 6 (0.8%) subjects who discontinued any oteseconazole dose due to AEs compared to one (0.3%) placebo subject who had influenza. These discontinuations included the case of allergic dermatitis in CL-017 as above. There was an additional case of allergic dermatitis reported in CL-006 with onset on day 9 which was also considered oteseconazole-related and led to discontinuation. However, this case was of moderate severity and it resolved by day 45. One subject discontinued oteseconazole in CL-011 due to vaginal infection and two subjects discontinued oteseconazole in CL-012 due to abdominal distension (considered unrelated) and blister (considered related and resolved). The sixth subject who discontinued due to an AE was enrolled into CL-006 and developed pancreatitis that was considered unrelated.

The applicant identified several AESIs that appear to have been selected on the basis of the safety profiles of other azole antifungal agents. The overall picture of reported AEs and laboratory abnormalities does not suggest a major risk of hepatotoxicity for oteseconazole. However, the current safety database is relatively small and the risk of hepatotoxicity should be reassessed in each PSUR.

In the RVVC pool, 12 subjects in oteseconazole group had ADRs that took an unusually long time (at least 56 days) to resolve, including 4 ADRs which were ongoing at the last visit. However, after detailed review of these cases, the evidence pointing to causality of oteseconazole was lacking or doubtful.

There has been one unrelated death in the programme.

SAEs have occurred at very low rates and have been judged unrelated to oteseconazole. No special risk for oteseconazole has emerged from these data.

In addition to the effects on transaminases, graded abnormalities in blood glucose occurred more often with oteseconazole vs. placebo in CL-017 (any grade 41% vs. 28%). These abnormalities were mostly high glucose but there were some cases of abnormally low glucose with a slightly higher rate with oteseconazole. However, although non-fasting levels were determined in all three Phase 3 studies, in CL-011 the percentages with any graded abnormal glucose value were 34% vs. 31% and respective rates were 30% vs. 33% in CL-012. Moreover, across the Phase 2/3 RVVC studies abnormal glucose values have been reported as AEs in very few subjects, with no excess for oteseconazole. Thus, the finding in CL-017 stands alone. Further investigation did not explain this difference between studies, which may have arisen by chance.

The applicant explored the safety database for effects of intrinsic factors. Effectively, there is no clinical experience in subjects aged <18 years (the indication is confined to adults) or in subjects aged >65 years (in which population RVVC is not a common issue but there is no reason to impose an upper age limit for use). There was no important effect of age on the oteseconazole safety profile between 18 and 64 years. While AE reporting rates differed between racial groups there was no major imbalance for oteseconazole vs. placebo within each racial group.

There is a recognised risk of hypersensitivity associated with use of triazoles and imidazoles. There have been reports of anaphylaxis and severe skin reactions (e.g. SJS and TEN) with these agents as well as less severe reactions such as rashes and urticaria. Oteseconazole is a tetrazole. The safety database for oteseconazole is too small at present to ascertain the risk but the occurrence of severe hypersensitivity reactions is to be expected and these may need prolonged medication to control them due to slow elimination. Meanwhile, the applicant has interrogated the safety database for possible hypersensitivity events but there are few cases and it is not possible to determine if there is any excess risk for oteseconazole vs. placebo. Some rashes were attributed to concomitant medications by investigators.

Oteseconazole was recently approved for prevention of RVVC in the US. The applicant provided information on the very few reports of ADRs received thus far, which did not suggest any need for further action or for additions to section 4.8 of the SmPC.

Implications of the elimination half-life for safety

The extremely long terminal elimination half-life has implications for time to resolution and management of some types of ADRs, with a specific concern regarding hypersensitivity reactions. This concern is somewhat exacerbated by the fact that there is no known means of accelerating the elimination of oteseconazole. The SmPC contraindicates use in any subject with hypersensitivity of any nature to triazole or imidazole drugs.

The applicant accepted removal of a statement to the effect that pregnancy could be considered after 2 y 7 m had elapsed from start of oteseconazole. However, there remains a statement in the list of contraindications that women who still have the capacity to become pregnant by means of assisted reproduction methods could consider pregnancy when 2 y and 8 months had elapsed, which is also rejected and must be removed.

ADRs in the SmPC

The applicant revised the proposal for section 4.8 as requested during the procedure.

3.3.9. Conclusions on clinical safety

There are no major objections based on the observed clinical safety profile. There are some potential safety issues arising from the nonclinical data and the extremely long terminal elimination half-life of oteseconazole, which likely reflects extensive distribution into tissues. These have been dealt with via statements in various parts of the SmPC.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

Although not requested in the D120 LOQ, the applicant has made the following change to Table SVIII.1. in the section on important potential risks:

Table SVIII.1 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Reproductive toxicity (off label use in women of childbearing potential)
Missing information	None

3.4.1.1. Discussion on safety specification

Having considered the data in the safety specification it is agreed that the safety concern listed by the applicant as an important potential risk is appropriate since this seems to be the only issue that can be addressed by anything other than routine PV. However, the change that has been made to table SVIII.1 is not acceptable. The applicant must remove the wording in the brackets.

3.4.1.2. Conclusions on the safety specification

It is agreed that the safety concerns listed by the applicant are appropriate, but the table requires amendment.

3.4.2. Pharmacovigilance plan

The Applicant proposes routine pharmacovigilance activities to monitor the safety concern: reproductive toxicity supplemented with a specific follow-up questionnaire, which aim is to collect information on the outcome of the pregnancy and the development of the child after birth where the embryo or foetus may have been exposed to Vivjoa.

No need to prepare separately breastfeeding form. However, the Applicant is asked to include breastfeeding in the name of FU questionnaire. Currently, in Part III section 2. Condition of newborn there is only question: Breast-feeding: ☐ Yes ☐ No; Comments. Therefore, the Applicant is asked to include the questions: If yes, was the mother receive oteseconazole while breast-feeding? ☐ Yes ☐ No; If yes, provide age at first exposure: ☐ Neonate ☐ Other Please specify; If yes, provide length of exposure.

In relation to reproductive toxicity, no need to discuss a pregnancy registry when the product is indicated for permanently infertile women. There is a possibility for off label use in women of childbearing potential, including women in whom pregnancy could potentially be achieved by any means of assisted reproduction (including use of stored eggs/embryos or use of donor eggs). To avoid off label use, the Patient alert card and Healthcare professional guide are proposed. Evaluation of effectiveness of risk minimisation should be assessed. Therefore, the Applicant was requested to provide a feasibility assessment for a drug utilisation study undertaken in the EU; and as applicable also provide a synopsis for such study. The Applicant has argued that a drug utilisation study is not feasible with currently available sources and believes that any such analysis attempt initiated in the near future would fail to provide conclusive evidence for lack of off-label usage.

Bearing in mind the Applicant's feasibility assessment of a drug utilisation study, the PRAC reporter considers that the effectiveness of additional RMMs, i.e. Healthcare professional guide and Patient alert card, should be measured by routine pharmacovigilance activities during PSUR preparation, as per the EURD list and signal detection activity as per internal procedures and evaluation of the effectiveness of additional RMMs should be provided in PSURs.

3.4.3 Risk minimisation measures

Routine Risk Minimisation Measures

Safety concern	Routine risk minimisation activities
Reproductive toxicity (off label use in women of childbearing potential)	*Routine risk communication:* SmPC section: 4.3, 4.6, 5.3 PL section: 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk* Contraindication in women of childbearing potential is provided in SmPC section 4.3. Exclusion of pregnancy prior to initiation of the treatment in SmPC section 4.6. *Other routine risk minimisation measures beyond the Product Information:*

Safety concern	Routine risk minimisation activities
	Prescription only medicine

The description of routine risk minimisation measures should be adjusted to indication, contraindication and section 4.6 of the SmPC accepted by CHMP.

Additional risk minimisation measures

Educational materials to prescribers for risk of Reproductive toxicity (off label use in women of childbearing potential)

Objectives and rationale: to inform the prescribers about:

- contraindication in women of childbearing potential,
- assisted reproduction technology cannot be initiated for 2 years and 8 months (32 months) from the treatment start due to unique half-life of Vivjoa and long elimination period,
- to visually present the treatment regimen schedule to reinforce a good treatment compliance of patients.

Target audience and planned distribution: all prescribers of Vivjoa are provided with educational materials at launch and thereafter (electronically).

Plans to evaluate the effectiveness of the interventions and criteria for success: monitoring of cases from post-marketing and reporting any off-label use in women of childbearing potential in PSURs.

Patient alert card for risk of Reproductive toxicity (off label use in women of childbearing potential)

Objectives and rationale: to inform the patients about:

- contraindication in women of childbearing potential,
- contraindication for assisted reproduction technology within 2 years and 8 months (32 months) from the treatment start,
- and to allow tracking treatment regimen.

Target audience and planned distribution: women with Vivjoa prescription. The distribution is through product package (including the Patient alert card in the Vivjoa package).

Plans to evaluate the effectiveness of the interventions and criteria for success: monitoring of cases from post-marketing and reporting any off-label use in women of childbearing potential in PSURs.

In RMP ver. 0.2, the Applicant provided revised key elements of the proposed educational materials (see above). The proposed key elements of educational materials are not consistent with CHMP position regarding contraindication. Therefore, should be revised (see List of outstanding issues).

Table Part V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Reproductive toxicity (off label use in women of childbearing potential)	Routine risk minimisation measures: - SmPC section 4.3 Contraindications - SmPC section 4.6 Fertility, pregnancy and lactation - SmPC section 5.3 Preclinical safety data - PL section 2 Warnings and precautions Additional risk minimisation measures: - Educational materials to prescribers - Patint alert card (in package)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: - Targeted follow-up questionnaire Additional pharmacovigilance activities: none

3.4.4 Summary of the risk management plan

The public summary of the RMP requires revision (see List of outstanding issues).

3.5. Pharmacovigilance

3.5.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

3.5.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the EBD or IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

Acute vulvo-vaginal candidiasis (AVVC) is a global health condition that affects approximately 75% of women at least once in their lifetime, most commonly when they are of childbearing age. Primary symptoms of VVC include itching/burning, irritation, inflammation, abnormal vaginal discharge, dysuria and painful sexual intercourse. Between 70–90% of VVC cases are caused by *Candida albicans*, with infections caused by *C. glabrata* accounting for 10–20% of cases. Less frequently, *C. krusei, C. parapsilosis* and *C. tropicalis* have been reported as the causative pathogen. Since oestrogen is known to increase the glycogen concentration of the vaginal lining and as glycogen is a substrate on which *C. albicans* thrives, VVC infections are lower in pre-menarche and postmenopausal female subjects and highest in women of childbearing potential (WOCP). Additional predisposing factors for VVC include lowered immunity due to HIV, steroid therapy, uncontrolled diabetes, sexual activity with an infected partner, use of oral or some barrier forms of contraception, use of HRT in post-menopausal women and recent use of antibacterial agents.

About half of women with AVVC experience a post-treatment recurrence and 5-9% of those with recurrence develop RVVC. RVVC has been variably defined as at least 3 or 4 symptomatic episodes in the previous 12 months.

4.1.2. Available therapies and unmet medical need

AVVC can be treated locally with topical imidazole antifungal agents (e.g. clotrimazole). Alternative treatment options for non-pregnant women are oral triazoles (e.g. fluconazole). Uncomplicated AVVC is typically treated with a short-course topical agent for 1-7 days or a single oral dose of fluconazole. These regimens provide a clinical and mycological cure rate of approximately 80%. These approaches are often insufficient for treatment of recurrences in women with RVVC. In Europe, fluconazole is indicated for prophylaxis to reduce the incidence of recurrences in women with RVVC using fluconazole 150 mg on days 1, 4 and 7 to address the presenting episode of AVVC followed by 150 mg once weekly for 6 months to prevent further recurrences. Nevertheless, Sobel *et al*. reported that within 6 months of completing such a course of fluconazole a recurrence occurred in 57%, with about half of cases having onset within 3-4 months.

4.1.3. Main clinical studies

Oteseconazole (VT-1161) is a tetrazole inhibitor of fungal lanosterol demethylase (CYP51) that has been evaluated for the treatment of an acute episode of AVVC and for prevention of recurrence in women who have RVVC. It is presented for clinical use as 150 mg hard capsules. Manufacture of capsules for the EU is proposed to occur at the applicant's facilities. The capsules used in the Phase 3 studies in women with RVVC were manufactured in Canada.

For the prevention of recurrent vulvovaginal candidiasis in women with RVVC, there was one dose-finding Phase 2 study (**CL-006**) and three Phase 3 studies (**CL-011, -012** and -**017**). Due to the very long terminal elimination half-life of oteseconazole in plasma, the applicant projected that less than 6 months maintenance treatment might provide a longer recurrence-free period after the last dose compared to the approved fluconazole regimen.

For that reason, and due to lack of sound PK-PD approaches for selecting doses for treatment of VVC, CL-006 compared 150 mg or 300 mg, each given initially for 7 consecutive days and then weekly for 12 weeks or 24 weeks. The results suggested no added benefit of the higher dose or the longer duration on recurrence rates. Therefore, Phase 3 studies used maintenance dosing with 150 mg weekly for 11 weeks (10 doses) after a loading dose regimen.

Only CL-017 used the exact final recommended posology with a loading dose (also used to treat the presenting AVVC episode) of 600 mg on day 1, 450 mg on day 2 and then 150 mg weekly starting on day 14 for 11 weeks (10 doses). In CL-011 and CL-012, after treatment of the presenting episode of AVVC with fluconazole (3 doses of 150 mg), the oteseconazole loading dose was 150 mg QD for 7 days after which 150 mg weekly dosing started on Day 14 as in CL-017.

For the treatment of the presenting episode of AVVC in women with RVVC, the data from **CL-017** are pivotal since this was the only study in which oteseconazole 600 mg plus 450 mg on consecutive days was compared to 3 doses of fluconazole for the treatment of AVVC in women with RVVC.

The main features of the three Phase 3 studies were very similar, including the selection criteria, the definitions of RVVC, response to treatment of AVVC and primary endpoint and the duration of follow-up for capturing recurrences (during maintenance dosing and for 36 weeks after last maintenance dose).

Randomisation into CL-017 occurred on confirming the AVVC episode in otherwise eligible women with RVVC. Randomisation was to treatment of AVVC with oteseconazole 600 mg on day 1 and 450 mg on day 2 followed by weekly maintenance dosing with 150 mg, or to treatment of AVVC with fluconazole (3 doses of 150 mg 72 h apart) followed by placebo weekly. Only those women who responded clinically (reduction in score to <3 on Day 14) continued into the maintenance phase to receive weekly dosing. In contrast, all women who consented at the screening visit in CL-011 and -012 received fluconazole (3 doses of 150 mg 72 h apart) for treatment of AVVC and only those who had a clinical response on day 14 were randomised into these studies to receive the 7-day loading dose regimen and then once weekly maintenance with oteseconazole, or placebo.

4.2. Favourable effects

Prevention of recurrence of AVVC in subjects with a history of RVVC

Based on the applicant's primary analysis, which employed multiple imputation and reported average percentages with at least one protocol-defined recurrence (culture–verified to be due to Candida with a signs and symptom score ≥3), each of the Phase 3 studies demonstrated that the oteseconazole regimens studied achieved statistically significant reductions in the proportion of women with at least one protocol-defined recurrence during the maintenance phase (including the weekly dosing and post-treatment follow-up). The magnitude of treatment effect was similar across the three studies.

In CL-017, the study population had a median of 3-4 prior episodes of AVVC, including the presenting episode, and 10-20% of subjects had 6-20 prior episodes. The average percentage with at least one recurrence of culture-verified AVVC by week 50 (i.e. counting any recurrences from baseline so including any within 14 days of randomisation) was 5.1% in the oteseconazole group and 42.2% in the control group. When counting recurrences only from day 14 to week 50 (i.e. during the 48 weeks of the maintenance phase), the average percentages with culture-verified AVVC were 3.8% vs. 41.1%, respectively.

The sensitivity analyses were supportive. Importantly, when subjects with missing data were counted as failures, the recurrence rate was 29.9% (Clopper Pearson 95% CI 22.7%, 38.0%) for oteseconazole vs. 55.6% (43.4%, 67.3%) for placebo, which was a statistically significant difference. Also supportive were the average percentages for recurrences when subjects who took any medication known to treat VVC were counted as failures (38.4% oteseconazole and 58.3% placebo; p=0.009). These sensitivity analyses were repeated counting proportions with recurrence from day 14 for the 185 subjects who entered the maintenance phase. When subjects with missing data were counted as failures, the recurrence rates calculated using the ITT population numbers as denominators were 22.6% for oteseconazole and 50.8% for placebo (p=<0.001).

A supplementary table shows the cumulative observed recurrences up to week 50 and reports 4 recurrences in the oteseconazole group and 24 in the placebo group. These numbers give rates of 3% vs. 40% for the 120 (82% of ITT population) oteseconazole and 60 (83% of ITT population) placebo subjects who attended the week 50 visit. The calculated rates are 2.7% vs. 33% when using the ITT denominators. As would be expected, almost all (24/28) of these recurrences involved *C. albicans*. Few subjects were considered to have had a recurrence until 2-3 weeks after randomisation, with about half of all first recurrences occurring before end of the maintenance treatment phase (week 14 from randomisation) and the majority occurring before week 20.

The average percentages with scores ≥3 regardless of culture results were 43.3% for oteseconazole vs. 64.6% for placebo, with a statistically significant difference. The rates for positive cultures regardless of scores by visit in the ITT population were consistently higher than rates for the primary endpoint, such that by week 50 the cumulative percentages were 22/120 (18%) for oteseconazole and 43/60 (72%) for placebo based on the numbers that attended the visit. Based on ITT denominators, the rates would be 15% vs. 60%. Since Candida *spp*. is commonly found in normal vaginal flora in specimens obtained from asymptomatic women, it is not surprising that rates for positive cultures exceeded those for protocol-defined culture-verified AVVC. However, it is noted that weekly oteseconazole suppressed detectable Candida in vaginal specimen cultures.

There were 4 ITT subjects (3%) in the oteseconazole group who had 1 culture-verified episode and none had >1 episode meeting the primary endpoint definition. In contrast, 14 (19%), 2 (3%), 6 (8%) and 2 (3%) ITT subjects in the placebo group had 1, 2, 3 or 5 culture-verified episodes, respectively. Also, in the ITT population, the mean number of times a subject was treated for VVC during the maintenance phase (noting that investigators could treat episodes that did not meet the full primary endpoint definition) was 0.7 in the oteseconazole group vs. 1.3 in the placebo group (p=0.043).

In the mITT population (46 oteseconazole and 21 placebo), which included only subjects with a positive screening culture who entered the maintenance phase with a negative culture on day 14, the average percentages with recurrence were 0% for oteseconazole vs. 55.7% in the placebo group.

In the sub-population of 63 oteseconazole and 25 fluconazole subjects that entered the maintenance phase with a zero signs and symptoms score on day 14, the average percentages with recurrence were 3.8% for oteseconazole vs. 52.8% for placebo.

In CL-011 and CL-012, based on average percentages, the magnitude of treatment effect was comparable and both demonstrated a statistically significant difference in the recurrence rate between oteseconazole (6.7% in CL-011 and 3.9% in CL-012) and placebo (42.8% and 39.4%, respectively). The planned sensitivity analyses of the primary endpoint supported the primary analysis.

In particular, with Missing=Failure, the proportions with at least one protocol-defined recurrence were 25.8% vs. 51.4% in CL-011 and 21.1% vs. 48.1% in CL-012, which were statistically significant differences. The tabulations of cumulative numbers with at least one recurrence meeting the primary endpoint definition also support the findings of the applicant's primary analyses. In CL-011 there were 14 (7%) vs. 45 (42%) with recurrences by week 48. In CL-012 there were 8 (4%) vs. 39 (36%) with recurrences by week 48.

The Kaplan-Meier plots indicated that the majority of recurrences in the placebo groups occurred during the first 12-18 weeks. The majority of recurrences were associated with *C. albicans*.

For the subsets (just over half of the ITT population) in each study with a signs and symptoms score of zero at randomisation, the average percentages with recurrence were 7.1% vs. 37.6% in CL-011 and 4.3% vs. 36.3% in CL-012. Both studies showed lower rates of treatment with any agent for AVVC in the oteseconazole group. Also, lower proportions in the oteseconazole groups had at least one positive culture for Candida (i.e. regardless of symptom score) or a score ≥3 (i.e. regardless of culture) during the maintenance phase.

Loading dose regimen for prevention of recurrence

The SmPC recommends only the loading dose regimen that was used in CL-017, in which oteseconazole 150 mg QW was started on day 14 after dosing with 600 mg on day 1 and 450 mg on day 2. This 2-day regimen was intended for treatment of the presenting episode of AVVC (on which see below) but it also served as a loading dose for the weekly regimen that started on day 14. Further simulations using the updated POPPK model suggested that there was no appreciable difference in exposures on day 14 after the two loading regimens and the simple 2-day regimen was accepted.

Treatment of AVVC in subjects with a history of recurrent VVC

Subjects with a history of RVVC and with a screening visit episode of AVVC were randomised to receive oteseconazole (600 mg on day 1 and 450 mg on day 2) or fluconazole (3 doses of 150 mg given 72 h apart) in a double dummy fashion. The 2-dose oteseconazole treatment regimen also served as a loading dose for the weekly oteseconazole maintenance regimen. The 3-dose fluconazole regimen is acceptable as a comparative regimen for evaluating oteseconazole for treatment of AVVC in women with a history of RVVC.

On ~day 14 from randomisation, in the PP population that was designated primary, the average percentage (derived using the MI approach) with resolution of AVVC (clinical response based on achieving a signs and symptoms score <3), was 93.1% for oteseconazole vs. 98.3% for fluconazole, with Wald 95% CI -10.7%, 0.2%. On this basis, and with a pre-defined NI margin of -15%, the applicant claims that non-inferiority was demonstrated.

When subjects with missing day 14 data were counted as failures or were excluded, the AVVC resolution rates were 90.8% and 92.9%, respectively, for oteseconazole vs. 98.3% in both analyses for fluconazole, with lower 95% CI at -14.3 and -11.8. Again, the applicant's pre-defined margin for concluding NI was met.

While the PP population was designated primary, in the ITT population the reported average percentages for day 14 clinical response were 93.2% vs. 95.8% with a lower bound of the Wald 95% CI at -8.8%.

The induction phase mITT population had a positive screening culture and comprised 100 subjects (46% of all oteseconazole and 48% of all fluconazole subjects). In this population, the average percentages for day 14 clinical response were 98.5% for oteseconazole vs. 94.1% for fluconazole, with a lower bound of the Wald 95% CI at -4.1%.

In addition, the average percentages that reached scores of zero at day 14 were slightly higher for oteseconazole in the PP, mITT and ITT populations, with lower bounds of the Wald 95% CI at -12.2, -6.6 and -5.4, respectively. The average percentages with clinical signs and symptoms scores of zero plus negative cultures for *Candida* species at Day 14 were comparable between treatments.

4.3. Uncertainties and limitations about favourable effects

Prevention of recurrence of AVVC in subjects with a history of RVVC

At the time of the CHMP advice on studies CL-011 and -012, the multiple imputation (MI) statistical approach was proposed by the applicant for the handling of missing data. In order to impute the missing values, a set of common subject characteristics (i.e. region, treatment, visit, baseline BMI, age at baseline and ethnicity) were to be included in the imputation model. The applicant proposed to use these characteristics to provide unbiased estimates for the missing data points for the culture result and/or the signs and symptoms score in a single model to produce a complete dataset. This would be done 10 times and then the endpoint would be derived for each of the 10 complete data sets and those 10 complete datasets would be analysed using standard procedures for complete data and the 10 results would be combined to produce a single p-value.

In response, the CHMP noted that MI is based on the assumption of missing at random, which might be questionable for the Phase 3 trials. Specifically, whether or not data were truly missing at random could not be ascertained and it could be deemed unlikely. Nevertheless, the applicant persisted with the plan to use MI and this was reflected in the SAPs for the analyses of the recurrence rates in all three Phase 3 studies. Thus, the applicant's tables that show the analysis of the primary endpoint and the sensitivity analyses, as well as many of the tables concerning secondary endpoints, report the *average percentage*.

It is accepted that the CSRs present analyses of the primary endpoint as defined in the SAPs, i.e. in which missing values have been handled using MI. However, the approach based on Missing at Random assumes that the recurrence rate in subjects who dropped out was similar to that observed in similar subjects in the same treatment arm who remained in the study and is not verifiable. It also seems unlikely that dropouts in the oteseconazole arm would experience similar recurrence rates as subjects remaining on study in the placebo arm, noting also that the recurrence rate was not stable over time, i.e. in the Phase 2 and in all three Phase 3 studies it was a consistent finding that most of the first recurrences occurred early on in the studies, mainly during or shortly after completion of the 12-week treatment periods.

Despite these concerns, the tables that report the cumulative numbers of observed cases and the analyses in which a missing=failure approach was taken do support the applicant's conclusion form the pre-defined primary analyses in each of the Phase 3 studies. Therefore, while there remain some uncertainties with regard to the magnitude of treatment effect reported in the applicant's primary analyses, the sum total of data do support a conclusion that the regimens used in the three Phase 3 studies exert a statistically significant reduction in the recurrence rates compared to placebo.

Treatment of the presenting AVVC episode in CL-017

The evidence needed to support the use of oteseconazole to treat acute episodes of VVC in subjects with a history of RVVC was not discussed with the CHMP. The ability of the oteseconazole 2-dose regimen to treat AVVC was a designated secondary endpoint and was evaluated by determining non-inferiority of clinical resolution rates at day 14 vs. the licensed comparator fluconazole in ~200 female subjects. Since the applicant provides only one study that assessed treatment of AVVC, the results must be completely compelling to support approval. Currently, the evidence from this single study that evaluated treatment of AVVC is not sufficiently compelling.

4.4. Unfavourable effects

Safety database

The most relevant safety information comes from the Phase 2 (CL-006; in which 2/4 cohorts received 150 mg Q for 7 days as a loading dose and 1/4 cohorts received 150 mg weekly for 12 weeks) and Phase 3 (CL-011, 012 and 017) studies in women with RVVC. The applicant counts 746 women as exposed to oteseconazole in these 4 studies and 663/746 received the 1050 mg loading dose. Of the 663 subjects given a total loading dose of 1050 mg, only CL-017 provides safety data on 146 subjects who received 600 mg on day 1 and 450 mg on day 2. The potential effect on safety of the higher Cmax achieved with the 2-dose loading regimen vs. 150 mg QD for 7 days can be gauged by comparing the safety data for the first 14 days on study.

Safety profile

For the most part, the observed AEs and ADRs with oteseconazole do not suggest major safety concerns associated with the final recommended posology. With the 1050 mg loading dose, administered either as 150 mg QD for 7 days or as 600 mg followed by 450 mg, and with 150 mg once weekly, the overall reporting rates were generally comparable to those for the pooled placebo group. While severe AEs and AEs leading to discontinuation occurred slightly more frequently with oteseconazole vs. placebo, the actual rates were <5% and <1% across groups, respectively.

Leaving aside the AEs concerning the reproductive system and intercurrent genitourinary or other types of infections, headache and nausea figure prominently among the most common AEs reported. However, while nausea and several other gastrointestinal SOC AEs were slightly more common with oteseconazole, rates for headache were higher with placebo. With the exception of the 300 mg dose groups in CL-006, the total rates for reporting ADRs were comparable between the oteseconazole and placebo groups. The most frequently reported ADRs were nausea and headache.

There has been one unrelated death in the programme. SAEs have occurred at very low rates and have been judged unrelated to oteseconazole.

In Phase 2/3 RVVC studies there were 6 (0.8%) subjects who discontinued any oteseconazole dose due to AEs compared to one (0.3%) placebo subject who had influenza. Only one severe AE was considered to be oteseconazole-related, this being a case of allergic dermatitis in CL-017 with onset on day 1 that led to discontinuation of treatment and had resolved by the time of reporting.
There was an additional case of allergic dermatitis reported in CL-006 with onset on day 9 which was also considered oteseconazole-related and led to discontinuation. However, this case was of moderate severity and it resolved by day 45.

One subject discontinued oteseconazole in CL-011 due to vaginal infection and two subjects discontinued oteseconazole in CL-012 due to abdominal distension (considered unrelated) and blister (considered related and resolved). The sixth subject who discontinued due to an AE was enrolled into CL-006 and developed pancreatitis that was considered unrelated.

There is effectively no clinical experience in subjects aged <18 years (the indication is confined to adults) or in subjects aged >65 years (in which population RVVC is not a common issue but there is no reason to impose an upper age limit for use). There was no important effect of age on the oteseconazole safety profile between 18 and 64 years. While AE reporting rates differed between racial groups there was no major imbalance for oteseconazole vs. placebo within each racial group. Whereas higher weight/BMI is associated with lower plasma exposures, the safety profile and the magnitude of difference for oteseconazole vs. placebo for prevention of recurrence was similar across the three Phase 3 studies even though the population in CL-017 was heavier and had lower exposures.

4.5. Uncertainties and limitations about unfavourable effects

Issues arising from the safety profile

The applicant identified several AESIs that appear to have been selected on the basis of the safety profiles of other azole antifungal agents. The overall picture of reported AEs and laboratory abnormalities does not suggest a major risk of hepatotoxicity for oteseconazole. However, the current safety database is relatively small and the risk of hepatotoxicity should be reassessed in each PSUR.

Graded abnormalities in blood glucose occurred more often with oteseconazole vs. placebo in CL-017 (any grade 41% vs. 28%) but this pattern was not observed in CL-011 or -012. Moreover, across the Phase 2/3 RVVC studies abnormal glucose values have been reported as AEs in very few subjects, with no excess for oteseconazole. Thus, the finding in CL-017 stands alone. Nevertheless, the fact that blood glucose was obtained under non-fasting conditions applied in all the Phase 2/3 studies and there is no obvious explanation for the imbalance seen only in CL-017. After further investigations, it seems that the findings of CL-017 may have arisen by chance.

There is a recognised risk of hypersensitivity associated with use of triazoles and imidazoles. There have been reports of anaphylaxis and severe skin reactions (e.g. SJS and TEN) with these agents as well as less severe reactions such as rashes and urticaria. Oteseconazole is a tetrazole. The safety database for oteseconazole is too small at present to ascertain the risk but the occurrence of severe hypersensitivity reactions is to be expected and these may need prolonged medication to control them due to very slow elimination (see further below). Meanwhile, the applicant has interrogated the safety database for possible hypersensitivity events but there are few cases and it is not possible to determine if there is any excess risk for oteseconazole vs. placebo.

Implications of the very long elimination half-life

The extremely long terminal elimination half-life has implications for time to resolution and management of some types of ADRs, with a specific concern regarding hypersensitivity reactions. This concern is somewhat exacerbated by the fact that there is no known means of accelerating the elimination of oteseconazole. For this reason, the SmPC contraindicates use in any subject with hypersensitivity of any nature to triazole or imidazole drugs as well as those with known hypersensitivity to oteseconazole or to any of the excipients.

The revised SmPC restricts use to women with no childbearing potential. However, section 4.3 still allows use in women who can become pregnant via assisted reproduction when 2 years and 8 months have elapsed from start of treatment. This is completely unacceptable.

4.6. Effects Table

Effects Table for Vivjoa in preventing recurrence and treating AVVC in women with RVVC

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects – Prevention of recurrence						
Rate of AVVC	Average percentage (MI)	%	Vivjoa	Placebo	Derived from MI, not absolute recurrence rate	
			N=217 6.7%	N=109 42.8%	P=<0.001	CL-011
			N=218 3.9%	N=108 39.4%	P=<0.001	CL-012
			N=147 5.1%	N=72 42.2%	P=<0.001	CL-017
Favourable Effects – Treatment of AVVC in women with RVVC						
AVVC resolution	Day 14 clinical response Average percentage (MI)	%	Vivjoa	Diflucan	Secondary endpoint in single study	
	Induction phase PP population		93.1%	98.3%	95% CI -10.7, 0.2%	CL-017
	Induction phase PP population M=F		90.8%	98.3%	95% CI -14.3, 0.9%	CL-017
	Induction phase PP population M excluded		92.9%	98.3%	95% CI -11.8, 2.9%	CL-017
Unfavourable Effects						
	Phase 2/3 RVVC pool		Vivjoa 1050 mg loading dose (N=663) Vivjoa 150 mg QW for 12 weeks (N=475)	Placebo N=336	Pooled placebo shown here; rates are similar to those observed with placebo in individual studies	CL-011, 012, 017 and 006
AE		%	56.9% 56.2%	61.6%		
AE on treatment			35.6% 34.5%	42.6%		
AE post treatment			42.8% 43.4%	44%		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
ADR			5.4% 4.8%	6.5%		
Severe AE			3.8% 4.0%	2.7%		
SAE			2.1% 2.3%	3.0%		
Death			0.2% 0%	0%		
AE with interruption of treatment			0.5% 0.6%	0.9%		
AE with discontinuation of treatment			0.8% 0.8%	0.3%		

Notes: rates were similar for loading dose 150 mg QD for 7 days (CL-011, 012 and 006) and for 600 mg on day 1 and 450 mg on day 2 (CL-017)

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

Prevention of a recurrence in adult female patients with a history of RVVC

The primary and sensitivity analyses of recurrence rates support the utility of oteseconazole.

Treatment of AVVC in adult female patients with a history of RVVC

There is a Major Objection to the applicant's indication for use of oteseconazole (600 mg on day 1 and 450 mg on day 2) to treat AVVC episodes in women with a history of RVVC. A single Phase 3 study has been conducted, which does not provide compelling evidence of efficacy. In this study, resolution of the presenting AVVC episode at day 14 was a secondary endpoint. While the study sample size was determined to address this endpoint, this was based on a pre-defined 15% non-inferiority margin, which is not sufficiently conservative. Based on average percentages derived using the applicant's MI approach, the lower bound of the Wald 95% CI around the difference in clinical resolution rates at day 14 in the designated primary analysis population (PP) exceeded -10%. In the PP population, when subjects with missing day 14 data were counted as failures or were excluded, the AVVC resolution rates were lower for oteseconazole (90.8% and 92.9%) vs. fluconazole (98.3% in both analyses) with lower bounds of the 95% CI at -14.3 and -11.8.

Safety of oteseconazole

There are no Major Objections based on the observed clinical safety profile. There are potential safety issues arising from the nonclinical data and the extremely long terminal elimination half-life of oteseconazole, which likely reflects extensive distribution into tissues. These have been addressed via the SmPC.

4.7.2. Balance of benefits and risks

There is no Major Objection to the use of oteseconazole to prevent recurrences in women with RVVC based on the revised indication that restricts use to women with no childbearing potential. However, there is a Major Objection on grounds of safety because section 4.3 of the revised SmPC allows consideration of pregnancy in women who may conceive via assisted reproduction when 2 y and 8 months have elapsed since start of oteseconazole treatment, which is completely unacceptable.

Even with such a restriction, there will be a need for very carefully worded educational materials. These must reflect the fact that women considered to not have childbearing potential but who still have a uterus could potentially seek assisted reproduction methods to achieve pregnancy, which must be avoided.

There is a Major Objection to the usage of oteseconazole to treat presenting episodes of AVVC in women with a history of RVVC, due to insufficient evidence of efficacy.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable

4.8. Conclusions

The overall benefit /risk balance of Vivjoa is negative.