DRUP – Drug specific study manual for ERDAFITINIB (Balversa)

1. Drug specific in- and exclusion criteria

Erdafitinib specific criteria are highlighted in light grey.

Inclusion criteria	Yes	No	n.a.
1. Patients must be ≥18 years of age.			
2. Histologically-proven locally advanced or metastatic solid tumor, multiple myeloma, non-Hodgkin lymphoma or T-cell prolymphocytic leukemia, with symptomatic or radiological disease progression after standard anti-cancer therapy, or for whom no such treatment is available or indicated.			
a. *For patients with a primary brain tumor: histologically confirmed recurrent or de novo primary brain tumor, with unequivocal progression after prior therapy, at least 3 months after radiotherapy (either first line chemo-radiotherapy or re-irradiation), and with stable or decreasing dosage of steroids for at least 7 days prior to the baseline MRI scan.*			
3. Presence of an oncogenic mutation that can potentially be targeted by erdafitinib (please refer to the list of drugs and acceptable profiles for further definitions). A complete sequencing report, confirming the actionable mutation has to be submitted for patient enrollment.			
4. ECOG performance status 0-2			
5. Patients must have acceptable organ and bone marrow function measured within 4 weeks prior to administration of study treatment as defined below:			
a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L			
b. Hemoglobin > 5.6 mmol/l			
c. Platelet count > 75 x 10^9/L			
d. Total bilirubin < 2 x ULN			
e. Phosphate ≤ ULN (despite medical management of phosphate levels)			
f. AST (SGOT) and ALT (SGPT) < 2.5 x institutional ULN (or < 5 x ULN in patients with known hepatic metastases)			
g. Serum creatinine ≤ 1.5 × ULN or calculated or measured creatinine clearance ≥ 30 mL/min/1.73 m^2			
6. Objectively measurable disease (by physical or radiographic examination, according to RECIST v1.1 for patients with solid tumors, or according to IMWG, Lugano, RANO or GCIG criteria, resp., for patients with multiple myeloma, non-Hodgkin lymphoma and T-cell prolymphocytic leukemia, primary brain tumors or ovarian cancer in case of CA125-based evaluation).			

Inclusion criteria	Yes	No	n.a.
7. A new (obtained ≤2 months before inclusion, and without any type of anti-cancer therapy within those ≤2 months) fresh frozen tumor biopsy specimen for extensive biomarker testing is mandatory before the start of treatment with a targeted agent included in the protocol. Alternatively, fresh frozen tumor tissue acquired in the context of a standard care procedure may be used, provided that no systemic anti-cancer treatment was given between the procedure and start of study treatment within DRUP. The following exceptions are made: a) An exception is made for patients with a primary brain tumor or other tumor types with only intracerebral lesions, only if the mandatory DRUP pre-treatment biopsy for biomarker analysis cannot safely be obtained: i. The fresh frozen tumor biopsy sample may be replaced by fresh frozen tumor tissue, obtained earlier from recurrent disease, as part of standard of care surgical procedure (i.e., performed at progression). ii. If no fresh frozen tumor tissue is available for NGS, and the risk of obtaining a new tumor biopsy is considered too high, no biopsy will be required. In this case, the study coordinators must be informed in advance, and there will be no reimbursement for the biopsy procedure. b) In case WGS is performed on tumor tissue outside the context of a clinical trial before inclusion, and without any type of anti-cancer therapy between the collection of tissue and inclusion in DRUP, this can replace the DRUP pre-treatment biopsy, provided that the patient gives consent to use his/her WGS data for biomarker analysis in DRUP. c) An exception is made for patients that underwent an allogenic hematopoietic stem cell transplantation prior to study enrollment, since this will prevent a correct WGS analysis due to a mismatch between the biopsy specimen and the required blood sample.			
8. Ability to understand and the willingness to sign a written informed consent document.			
9. For orally administered drugs, the patient must be able to swallow and tolerate oral medication and must have no known malabsorption syndrome.			
10. Women of child-bearing potential must agree to use highly effective (i.e. IUD/IUS, hormonal implants, abstinence or male partner who has undergone vasectomy with confirmed azoospermia) for the duration of study participation, and for 3 months following completion of study therapy. Women using oral hormonal contraceptives should add a barrier method for contraception purposes.			

Exclusion criteria	Yes	No	n.a.
1. Patients that are eligible for on-label treatment with erdafitinib or for ongoing phase 2 / 3 trials with erdafitinib are excluded from treatment with erdafitinib within the DRUP trial.			
2. Known hypersensitivity to the active substance or to any of the excipients.			

Exclusion criteria	**Yes**	**No**	**n.a.**
3. Active malignancies other than for the disease being treated under study. An exception is made for: a. Skin cancer treated within the last 24 months that is considered completely cured b. History of localized breast cancer and receiving antihormonal agent c. History of localized prostate cancer and receiving androgen deprivation therapy			
4. Known with central serous retinopathy or retinal pigment epithelial detachment of any grade			
5. Ongoing toxicity ≥ grade 2, other than alopecia or grade 2 peripheral neuropathy.			
6. Patient is receiving any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement). Required wash out period prior to starting study treatment is at least two weeks. An exception is made for patients suffering from CRPC, who are allowed to continue androgen deprivation therapy.			
7. Patient is pregnant or nursing.			
8. Patients with brain metastases. Patients with previously treated brain metastases are eligible, provided that the patient has not experienced a seizure or had a clinically significant change in neurological status within the 3 months prior to registration. All patients with previously treated brain metastases must be stable for at least 1 month after completion of treatment and off steroid treatment prior to study enrollment.			
<u>*For glioblastoma patients*</u>*:* *a. Patients who require anti-convulsant therapy must be taking non-enzyme inducing antiepileptic drugs (non-EIAED). EIAED are prohibited. Patients previously on EIAED must be switched to non-EIAED at least 2 weeks prior to randomization.* *b. No radiotherapy within the three months prior to the diagnosis of progression.* *c. No radiotherapy with a dose over 65 Gy, stereotactic radiosurgery or brachytherapy unless the recurrence is histologically proven.*			
9. Patients with clinically significant preexisting cardiac conditions, including uncontrolled or symptomatic angina, uncontrolled atrial or ventricular arrhythmias, or symptomatic congestive heart failure are not eligible.			
10. Patients with impaired wound healing capacity, defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unheald incisions.			
11. Patients with known left ventricular ejection fraction (LVEF) < 40% are not eligible.			
12. Radiation therapy ≤ 21 days prior to start study treatment. Subjects must have recovered from all radiation-related toxicities and/or complications prior to treatment. a. An exception is made for completed palliative radiotherapy to bone lesions ≥ 2 weeks prior the start of the treatment.			
13. Patients with stroke (including TIA) or acute myocardial infarction within 3 months before the first dose of study treatment are not eligible.			

Exclusion criteria	Yes	No	n.a.
14. Patients with any other clinically significant medical condition which, in the opinion of the treating physician, makes it undesirable for the patient to participate in the study or which could jeopardize compliance with study requirements including, but not limited to: ongoing or active infection, significant uncontrolled hypertension, or severe psychiatric illness/social situations.			

NB Please note that official prescription instructions, as outlined in the Summary of Product Characteristics (SPC, most recent version can be downloaded from https://www.ema.europa.eu/en/medicines) and / or any other official documents concerning this drug, will always take precedence over this manual. This manual is provided for practical support; treatment can be performed according to local standard-of-care protocols.

2. Treatment schedule

	Screening (≤28 days before start)	After screening, before start	D1 of every treatment cycle (1 cycle = 28 days)	D14 – 21 of first treatment cycle	At the end of every 2nd treatment cycle	After end of treatment (≤30 days after stop)
Concurrent meds	X		X			
Adverse events			X			
Physical exam	X		X[1]			
Vital signs	X		X[1]			
Performance Status	X		X			
Ophthalmological examination	X[2]		X[2]			
OCT	X[3]					
Hb, neutrophil count, platelets	X		X[1]			
Serum chemistry and endocrinology	X[1]		X[1]			
Serum Phosphate			X[4]	X[4]		
Pregnancy test	X[5]					
Tumor biopsy		X[6]				X[6]
Erdafitinib			X (continuous dosing)	X[7]		
Response evaluation	X[8]				X[8]	

1. According to local standard clinical practice, or as clinically indicated
2. The opthalmological examinations must be performed by an ophthalmologist and should include assessment of visual acuity, slit lamp examination, fundoscopy, Amsler Grid test, and slit lamp biomicroscopy . The examinations must be performed monthly during the first four months, every 3 months afterwards, and at any time for visual symptoms.
3. An Optical Coherence Tomography (OCT) must be performed at screening and as clinically indicated
4. Serum phosphate (PO_4) levels should be assessed at screening and between 14 – 21 days after start study treatment, thereafter phosphate levers should be assessed on D1 of every treatment cycle
5. Woman of childbearing potential must have a negative pregnancy test within 7 days before start study treatment
6. Tumor biopsy: after screening is positive, a mandatory DRUP pre-treatment biopsy should be taken. After termination of DRUP treatment, a post-treatment biopsy can be taken. The post-treatment biopsy is optional.
7. Increase the dose of erdafitinib to **9mg** (three 3mg tablets) once daily, if possible, based on serum phosphate (PO4) levels and tolerability after 14 – 21 days (please refer to section 3. Administration and starting dosage).

8. A baseline scan should be performed <28 days before start of treatment. Tumor assessments will initially be repeated every 8 weeks after treatment initiation. If the patient continues study treatment beyond 3 response evaluations (i.e., 24 weeks), response evaluation will thereafter be performed at the end of every 12 weeks.

3. Administration and starting dosage

The recommended starting dose of erdafitinib is **8 mg** (two 4 mg tablets) orally once daily, with a dose increase to **9 mg** (three 3 mg tablets) once daily based on serum phosphate (PO4) levels and tolerability assessed at 14 – 21 days after initiation of treatment.

Swallow tablets whole with or without food. If vomiting occurs any time after taking erdafitinib, the next dose should be taken the next day. Treatment should continue until disease progression or unacceptable toxicity occurs.
If a dose of erdafitinib is missed, it can be taken as soon as possible on the same day. Resume the regular daily dose schedule for erdafitinib the next day. Extra tablets should not be taken to make up for the missed dose.

Dose Increase based on Serum Phosphate Levels
Assess serum phosphate levels 14 – 21 days after initiating treatment. Increase the dose of erdafitinib to 9 mg once daily if serum phosphate level is < 9.0 mg/dL (< 2.91 mmol/L) and there is no drug-related toxicity. If the phosphate level is 9.0 mg/dL or higher follow the relevant dose modifications in Table 2.

Monitor phosphate levels monthly for hyperphosphatemia. After day 21 the serum phosphate level should not be used to guide the decision for a dose increase.

4. How supplied

Erdafitinib is supplied as 3, 4 or 5mg oral film-coated tablets. Drugs can be (re-)ordered by filling in the required fields in the eCRF. Drugs will be shipped to the site's pharmacy. Per shipment, sufficient drug can be ordered to treat the patient until the next response evaluation (and 1 cycle beyond for the first order, to cover the period in between response evaluation and re-supply).

Since dose increase is recommended after 14 days, sites will receive with the first drug order 2 bottles of 4 mg tablets and 1 bottle of 3 mg tablets. This corresponds to the recommended starting dose of 8 mg, and allows a dose increase to 9 mg after 14 days (if supported by serum phosphate levels and tolerability) or a dose reduction if necessary. After day 14 a drug re-order should be placed to order the correct doses (3, 4 or 5 mg tablets, depending on prescribed dose) for the further courses.

5. Dose modifications for toxicity

The recommended dose modifications for adverse reactions are listed in Table 1.

Table 1

Dose	1st dose reduction	2nd dose reduction	3rd dose reduction	4th dose reduction	5th dose reduction
9 mg	8 mg	6 mg	5 mg	4 mg	STOP
8 mg	6 mg	5 mg	4 mg	STOP	

6. Warnings and precautions

Please refer to the SPC for more detailed information.

Drug interactions

CYP2C9 and CYP3A4

CYP2C9 or CYP3A4 inhibitors: Co-administration with a moderate CYP2C9 or strong CYP3A4 inhibitor increased erdafitinib exposure and may lead to increased drug-related toxicity. Consider alternative agents with no or minimal enzyme inhibition potential. If erdafitinib is co-administered with a moderate CYP2C9 or strong CYP3A4 inhibitor, reduce the erdafitinib dose based on tolerability. If the inhibitor is discontinued, erdafitinib dose may be adjusted as tolerated. Moderate or strong CYP2C9 or CYP3A4 inducers: The impact of moderate CYP2C9 inducers and strong CYP3A4 inducers (such as rifampin) on erdafitinib was not clinically studied.

The concomitant use of moderate CYP2C9 inducers and strong CYP3A4 inducers with erdafitinib should be avoided as co-administration may significantly decrease erdafitinib exposure. Caution should be exercised for concomitant administration of erdafitinib and moderate CYP3A4 inducers as this may result in decreased erdafitinib exposure.

P-Glycoprotein substrates

Caution should be exercised for co-administered drugs that are P-gp substrates, such as digoxin, dabigatran, apixaban, etc. Concomitant administration of erdafitinib with P-gp substrates may increase their systemic exposure if administered concurrently. Oral narrow therapeutic index P-gp substrates such as digoxin should be taken at least 6 hours before or after erdafitinib to minimize the potential for interactions.

Hyperphosphatemia

Increases in phosphate levels are a pharmacodynamic effect of erdafitinib. Hyperphosphatemia was reported as adverse reaction in 78.5% of patients treated with erdafitinib. The median onset time for any grade event of hyperphosphatemia was 16 days after initiating erdafitinib. Thirty-two percent of patients received phosphate binders during treatment with erdafitinib.

Table 2

Hyperphosphatemia	**Erdafitinib Dose Modification**
For phosphate concentrations ≥5.5 mg/dL (1.75 mmol/L), restrict phosphate intake to 600 - 800 mg/day.	
<6.99 mg/dL (<2.24 mmol/L)	Continue erdafitinib at current dose.
7.00-8.99 mg/dL (2.25-2.90 mmol/L)	Continue erdafitinib. Start phosphate binder with food until phosphate level is <7.00 mg/dL. A dose reduction should be implemented for a sustained serum phosphate level of ≥7.00 mg/dL for a period of 2 months or in the presence of additional adverse events or additional electrolyte disturbances linked to prolonged hyperphosphataemia.
> 9.00-10.00 mg/dL (2.91-3.20 mmol/L)	Withhold erdafitinib with weekly reassessments until level returns to < 7.00 mg/dL (weekly testing recommended). Start phosphate binder with food until serum phosphate level returns to <7.00 mg/dL. Re-start treatment at the same dose level (see Table 1). A dose reduction should be implemented for sustained serum phosphate level of ≥9.00 mg/dL for a period of 1 month or in the presence of additional adverse events or additional electrolyte disturbances linked to prolonged hyperphosphataemia.
> 10.00 mg/dL (> 3.20 mmol/L)	Withhold erdafitinib with weekly reassessments until serum phosphate level returns to <7.00 mg/dL (weekly testing recommended). Re-start treatment at the first reduced dose level (see Table 1). If serum phosphate level of ≥10.00 mg/dL is sustained for >2 weeks, erdafitinib should be discontinued permanently.
Significant alteration from baseline renal function or Grade 3 hypocalcaemia due to hyperphosphataemia	Erdafitinib should be discontinued permanently. Medical management as clinically appropriate.

Recommendation regarding eye examinations

The ophthalmological examinations must be performed by an ophthalmologist and should include assessment of visual acuity, slit lamp examination, fundoscopy (examination of both central and

peripheral zones should be performed), Amsler grid test, and slit lamp biomicroscopy. An Optical Coherence Tomography (OCT) will also be performed at Screening.

When CSR/ retinal pigment epithelial detachments (RPED) is suspected then an OCT should be performed. Fluorescein angiography could be considered appropriate in conditions such as suspected retinal vein occlusion (RVO). It is also recommended that color fundus photos or OCT images be obtained and stored in the patient's file for future reference. In patients with suspected retinal pathology such as CSR or RVO a consultation with a retina specialist should be considered.

Management Guidelines for Eye Disorders Associated with Vision Changes

Any new eye symptoms of clinical significance such as but not limited to blurred vision, partial or complete loss of vision, double vision, floaters or color spots or halos around light, change in color or night vision, photophobia, ocular pain or stinging sensation, foreign body sensation should be further evaluated and managed as per the guidelines below.

Grade and definition	**Study drug management**	**Symptom management**
Grade 1: Asymptomatic or mild symptoms; clinical or diagnostic observations only Or abnormal Amsler grid test	Refer for an ophthalmologic examination. If an ophthalmologic exam cannot be performed within 7 days, withhold treatment with erdafitinib until an examination can be performed. If there is no evidence of eye toxicity on ophthalmologic examination, continue erdafitinib at the same dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as central serous retinopathy (CSR)/ retinal pigment epithelialdetachments (RPED), withhold erdafitinib until signs and symptoms have resolved. If toxicity is reversible (complete resolution or stabilization and asymptomatic) in 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level after consultation with the DRUP study team. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter. If there is no recurrence, then re-escalation can be considered in consultation with the DRUP team.	Refer the subject for an ophthalmologic examination. For retinal pathology perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.

Grade and definition	Study drug management	Symptom management
Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Immediately withhold erdafitinib and refer for an ophthalmologic examination. If there is no evidence of drug-related corneal or retinal pathology on ophthalmologic examination, withhold erdafitinib until signs and symptoms have resolved. Resume erdafitinib therapy at the next lower dose level. If diagnosis from ophthalmologic examination is keratitis or retinal abnormality such as CSR/RPED, withhold erdafitinib until signs and symptoms have resolved, stabilized, or subject is lost to follow-up or withdraws consent (which ever happens first). If toxicity is reversible (complete resolution or stabilization and asymptomatic) within 4 weeks according to ophthalmologic examination, resume erdafitinib at the next lower dose level after consultation with the DRUP study team. Monitor for recurrence every 1 to 2 weeks for a month and as clinically appropriate thereafter.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.
Grade 3: Severe or medically significant but not immediate sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL	If the toxicity is Grade 3, report as a serious adverse event and withhold erdafitinib. If the toxicity is Grade 3 and reversible (complete resolution or stabilization and asymptomatic) within 4 weeks and the subject is having clinical benefit, and the investigator and the sponsor's medical monitor agree that continuation of treatment is in the best interest of the subject, then drug may be resumed at 2 dose levels lower if appropriate. Monitor for recurrence using appropriate investigations every 1 to 2 weeks for a month and as clinically appropriate thereafter. For cases of recurrence, consider permanent discontinuation.	Refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. For retinal pathology, perform OCT as appropriate and consider referral to a retinal specialist for further evaluation. Follow specific treatment per the ophthalmologist's recommendation.

Grade and definition	Study drug management	Symptom management
Grade 4: Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	Permanently discontinue treatment with erdafitinib. Report as a serious adverse event and monitor resolution of the event until complete resolution, stabilization or the subject is lost to follow-up or withdraws consent (whichever happens first).	Promptly refer subject to an ophthalmologist for evaluation with an ophthalmologic examination. Follow specific treatment per the ophthalmologist's recommendation.

Management Guidelines for Dry Mouth and Oral Mucositis

Guidelines for Management of Dry Mouth (Xerostomia)

Grade and Definition	Study Drug Management	Symptom Management
Grade 1: symptomatic (eg, dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges as needed
Grade 2: moderate symptoms; oral intake alterations (eg, copious water, other lubricants, diet limited to purees or soft, moist foods); unstimulated saliva 0.1 to 0.2 mL/min	Continue study drug at current dose.	Sorbitol lozenges as needed and Cevimeline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 3: inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva less than 0.1 mL/min	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolved to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the medical monitor.	Sorbitol lozenges as needed and Cevimeline 30 mg TID or Pilocarpine 5 mg TID, orally
Grade 4: life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated

Guidelines for Management of Oral Mucositis

Grade	**Study drug management**	**Symptom management**
Grade 1	Continue study drug at current dose.	Continue general prophylaxis recommendations Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. Consider clotrimazole/nystatin if subjects are at risk of developing oral candidiasis.
Grade 2	Consider holding study drug if the subject has other study drug related concomitant Grade 2 AEs. Hold study drug if the subject was already on symptom management (dexamethasone solution swish and spit and lidocaine 2%-5% jelly or solution) for more than a week. If the study drug is withheld, reassess in 1-2 weeks. If this is the first occurrence of toxicity and resolves to ≤ Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes > 2 weeks to resolve to ≤ Grade 1 or baseline, then restart at 1 dose level.	Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2-5% jelly or solution. Consider concomitant etiologies such as oral candidiasis, oral herpes and appropriate antifungal or anti-viral agents.
Grade 3	Hold study drug, with reassessments of clinical condition in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the DRUP study team	Dexamethasone solution (0.5 mg/5mL solution) swish and spit QID or similar solution that is available in your country and lidocaine 2%-5% jelly or solution. Consider pain management strategies.
Grade 4	Discontinue study drug.	Evaluation and therapy as clinically indicated

Management Guidelines for Nail Discoloration/Loss/Ridging (Onycholysis/Onychodystrophy)

Grade	Study Drug Management	Symptom Management
Grade 1	Continue study drug at current dose.	Continue general prophylaxis recommendations Over the counter nail strengthener OR polyurea urethane nail lacquer (Nuvail™) OR diethylene glycol monoethylether nail lacquer daily (Genadur). Use non- alcohol containing moisturizing creams.
Grade 2	Consider holding study drug with reassessment in 1-2 weeks. If first occurrence and it resolves to ≤Grade 1 or baseline within 2 weeks, restart at same dose. If recurrent event or takes > 2 weeks to resolve to ≤Grade 1 or baseline, then restart at 1 dose level below in consultation with the DRUP study team	Manage as per grade 1 For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: 1. treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim BID) AND 2. topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) Silver nitrate application weekly AND topical antibiotics AND vinegar soaksa
Grade 3	Hold study drug, with reassessment in 1-2 weeks. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the DRUP study team.	Silver nitrate application weekly AND topical antibiotics AND vinegar soaks. For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: 1. Treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/trimethoprim BID). 2. For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.
Grade 4	Discontinue study drug.	Evaluation and therapy as clinically indicated.

Guidelines for Management of Paronychia

Grade	Study Drug Management	Symptom management
Grade 1	Continue study drug at current dose	Topical antibiotics AND vinegar soaks.
Grade 2	Continue study drug at current dose. Consider study drug holding if no improvement in 1 to 2 weeks. When resolves to ≤Grade 1 or baseline, restart at same or 1 dose level below in consultation with the DRUP study team	Topical antibiotics AND vinegar soaks AND topical antifungal lacquer daily for 6+ weeks (ciclopirox olamine 8% OR efinaconazole 10% OR amorolfine 5% weekly OR bifonazole/urea ointment daily) For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim DS BID).
Grade 3	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or baseline, restart at one dose level below in consultation with the DRUP study team.	Vinegar soaks AND consider nail avulsion For signs of infection (periungal edema/erythema/ tenderness or discharge), obtain bacterial cultures, and then start the following: treatment with oral antibiotic for 2 weeks (cefadroxil 500 mg BID, ciprofloxacin 500 mg BID, or sulfamethoxazole/ trimethoprim DS BID). For cases of severe/refractory infection consider intravenous antibiotics. Consider dermatological or surgical evaluation.
Grade 4	Discontinue study drug	Evaluation and therapy as clinically indicated.

Management Guidelines for Dry Skin and Skin Toxicity

Grade and Definition	**Study Drug Management**	**Symptom Management**
Grade 1: Dry skin covering less than 10% body surface area (BSA) and no associated erythema or pruritus	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/ hyperkeratotic areas such as palms and soles.
Grade 2: Dry skin covering 10% to 30% BSA and associated with erythema or pruritis with limited instrumental activities of daily living (IADL)	Continue study drug at current dose.	Use fragrance free moisturizing cream or ointment BID over entire body. Use ammonium lactate 12% cream or salicylic acid 6% cream BID over dry/scaly/ hyperkeratotic areas such as palms and soles. Use zinc oxide 13%-40% at night for areas with fissures.
Grade 3: Dry skin covering >30% BSA and associated with pruritis; limiting self-care activities of daily living (ADL)	Hold study drug (for up to 28 days), with weekly reassessments of clinical condition. When resolves to ≤Grade 1 or baseline, restart at 1 dose level below in consultation with the DRUP study team.	Use topical steroid ointment or cream BID and zinc oxide 13%-40% at night for areas with fissures.
Grade 4: Dry skin with life-threatening consequences, urgent intervention indicated	Discontinue study drug.	Evaluation and therapy as clinically indicated