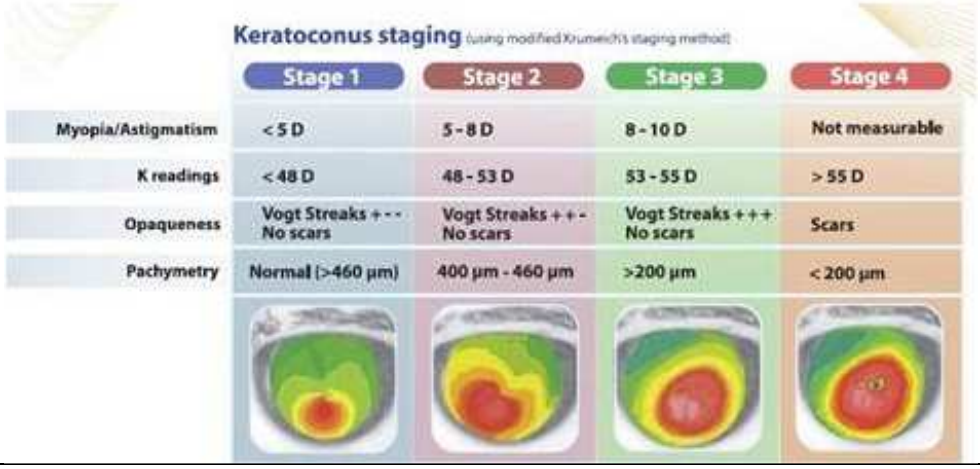
1.4.Synopsis

Title of the clinical investigation	**Performance and safety assessment of T4020 combined with standard post-operative therapy versus standard post-operative therapy in managing corneal epithelial defect following epi-off accelerated corneal crosslinking**
International Coordinating Investigator	Prof (Associate) Koray Gumus, Kayseri (Turkey)
Clinical investigation design	This is a prospective, randomised, double-masked, controlled, multicentre international clinical investigation
Clinical investigation objective(s)	**Primary objective**: To assess performance of T4020 combined with standard post-operative therapy versus standard post-operative therapy regarding corneal epithelial defect (CED) healing following epi-off accelerated corneal crosslinking (CXL) **Other objectives**: To assess ocular symptoms and safety
Clinical investigation endpoints	**Primary performance endpoint:** Response defined as complete healing of CED (absence of CED) as assessed by the investigator on Corneal Fluorescein Staining (CFS) at slit lamp examination. (A patient with complete healing of CED could still present superficial punctate keratitis [SPK] or stained healing lines). Two time points will be considered: Day 3 (D3) and Day 4 (D4). **Secondary performance endpoint:** - CED size assessed by the investigator on CFS at slit lamp examination after Contact Lens (CL) removal at D3, D4, and D5. **Other performance endpoints:** - Time to complete healing of CED. - Superficial punctate keratitis (SPK) (graded using the National Eye Institute [NEI] 0 - 15 scale) at D3, D4 and D5. - Presence or absence of stained typical healing lines at D3, D4 and D5. - Conjunctival staining (graded using the National Eye Institute [NEI] 0 - 18 scale) at screening visit and D5. - Total ocular pain score (graded on 0-10 Numeric Rating Scale) at D1, D2, D3, D4, and D5. - Each symptom including light sensitivity, burning / stinging, tearing, foreign body sensation (graded on 0-10 numeric rating scale: 0: absence of the symptom and 10: worst imaginable symptom) at D1, D2, D3, D4, and D5. - Sum of scores of light sensitivity, burning / stinging, tearing, foreign body

	sensation at D1, D2, D3, D4 and D5. - Use of painkillers at D1, D2, D3, D4 and D5. - Measurement of the CED on CFS photos by a reading center at D1, D3, D4, and D5 (ancillary). **<u>Safety endpoints:</u>** - Conjunctival hyperaemia (graded using the McMonnies grading [0 to 5]) at D3, D4 and D5. - Uncorrected visual acuity (UCVA) and far best corrected visual acuity (BCVA) (using a Snellen chart) at screening visit and D5 after CL removal. - Non-contact intraocular pressure (IOP) at screening visit and D5 (after CL removal). - Adverse events (AEs)/ Adverse Device Effects (ADEs) recorded throughout the clinical investigation by the investigator.
Investigational Product	T4020 will be combined with the standard post-operative therapy. **Dosing regimen:** one administration into the CXL eye every other day for 5 days: • The first one at surgery before fitting CL, • The second one at D3 (after the visit, on the CL) at the site, • The third one at D5 (in the morning at home before the visit, on the CL).
	Saline solution will be combined with the standard post-operative therapy. **Dosing regimen:** one administration into the CXL eye every other day for 5 days: • The first one at surgery before fitting CL, • The second one at D3 (after the visit, on the CL) at the site, • The third one at D5 (in the morning at home before the visit, on the CL).
Methodology	**<u>Randomisation:</u>** Patients will be randomised into two groups. In one group, T4020 will be used and, in the other group, saline solution will be used. <u>Auxiliary products and Therapies:</u> During the perioperative period, clinical investigation personnel will instil the drops. Then, the patients will instil the drops after they go home. All participants will be asked to use the same medications before and after the procedure as scheduled in the clinical investigation plan and detailed in the investigator manual: In addition to cutaneous anti-infective solution and the bandage contact lens, the standardised treatment will include topical anaesthetic, direct-acting cholinergic agonist, topical antibiotic and artificial tears. Topical corticosteroid will be started after complete corneal healing. Epi-off accelerated cross-linking with isotonic riboflavin will be performed as detailed in the protocol. Patients will be permitted to take oral paracetamol 1g for ocular pain and

	paracetamol 500mg with codein 30mg or equivalent in case of severe pain.
Number of patients	About 147 screened patients to obtain 132 evaluable patients.
Inclusion criteria	*[1.1]* Patient must provide signed and dated informed consent. *[1.2]* Male or female patient at least 18 years of age. *[1.3]* Patient with at least one eye: o with a progressive keratoconus (KC) occurring during the last 6 months according to the investigator judgement, o AND scheduled for an epi-off CXL procedure with no concomitant CXL in the other eye at the same time. *[1.4]* Corneal thickness ≥ 400 µm in the eye undergoing CXL. *[1.5]* KC staging I-II according to Amsler-Krumeich classification in the eye undergoing CXL: 
Exclusion criteria	**<u>2.1 Ophthalmic Exclusion Criteria:</u>** **<u>in the eye undergoing CXL:</u>** *[2.1.1]* Anesthetic / Hypoesthetic cornea < 20 mm with a Cochet-Bonnet aesthesiometer. *[2.1.2]* Ocular surface disease index (OSDI) scores > 23. *[2.1.3]* Schirmer test with anaesthesia < 10 mm/5min. *[2.1.4]* Tear Break-Up Time (TBUT) < 7 sec. *[2.1.5]* Corneal fluorescein staining score > 3 (NEI criteria). *[2.1.6]* Conjunctival staining score > 3 (NEI criteria). *[2.1.7]* Presence of any abnormalities preventing reliable measurements as judged by the investigator. *[2.1.8]* History of any ocular injury. *[2.1.9]* History within 1 month before the screening visit or any active ocular infection (e.g., bacterial, viral, fungal, acanthamoeba), ocular injury, and associated corneal ulceration and abscess, occurring during the screening period. **<u>at least in one eye:</u>** *[2.1.10]* History of any atopic keratoconjunctivitis (AKC), any active uveitis, or any other ocular disorder or condition that could be in the judgment of the investigator, jeopardize patient safety or interfere with the

	interpretation of clinical investigation results. *[2.1.11]* No active vernal keratoconjunctivitis (VKC) within 6 months including D1. *[2.1.12]* Ocular hypertension or glaucoma requiring an ophthalmic medicinal product. *[2.1.13]* History of ocular Herpes. *[2.1.14]* Far BCVA ≤ 2/10 Snellen. *[2.1.15]* Abnormal eye lid anatomy, blinking, or naso-lachrymal drainage system. **2.2 Systemic/non-ophthalmic exclusion criteria** *[2.2.1]* Known or suspected hypersensitivity to one of the components of: - the investigational products and/or heparinoids or heparin or - the auxiliary products: ofloxacin and other quinolones (eg ciprofloxacin, norfloxacin, moxifloxacin, levofloxacin), dexamethasone, povidone and iodine povidone, oxybuprocain and other local anaesthetics, cholinergic agonists, riboflavin and others chemical related susbtances, paracetamol, other ingredients of the mentioned medicinal products or medical devices, - the materials and medicinal products or medical devices used during standard ophtalmological examinations. *[2.2.2]* Any condition judged by the investigator to be incompatible with the clinical investigation or likely to interfere with the clinical investigation results e.g.: acute or chronic severe disease (hepatic, renal, endocrine, neoplasic, haematological disorder, immunosuppression, infectious diseases, severe psychiatric illness, relevant cardiovascular abnormalities, etc) and/or any other factor or abnormality. *[2.2.3]* On-going malignancy during the screening period or history of malignancy within 5 years before D1. *[2.2.4]* Any history of known clinically significant conditions: i. Graft-versus-host disease, transplanted patient. ii. Any other non-controlled systemic disorder. iii. History of drug addiction or alcohol abuse. **2.3 Specific exclusion criteria for women:** *[2.3.1]* Pregnancy or lactation. *[2.3.2]* Childbearing potential woman who is not using a reliable method of contraception (oral contraceptive, intra-uterine device, subcutaneous contraceptive implant, vaginal ring, patch) or is not surgically sterilised. **2.4 Exclusion criteria related to general conditions:** *[2.4.1]* Inability of patient and/or relatives to understand the clinical investigation procedures and thus inability to give informed consent. *[2.4.2]* Non-compliant patient and/or relatives (e.g. not willing to attend a visit, way of life interfering with compliance).

[2.4.3] Participation in the present clinical investigation at the same time as another clinical investigation.

[2.4.4] Participation in this clinical investigation within 4 weeks after the end of a previous clinical investigation (or within 5 half-life of the previously tested product if longer than 4 weeks).

[2.4.5] Patient previously randomised in this clinical investigation.

[2.4.6] Patient being institutionalised because of legal or regulatory order, inmate of psychiatric wards, prison or state institutions, or employee of the clinical investigation sites or of the Sponsor's company.

[2.4.7] Patient not covered by the government health care scheme when existing in the concerned country.

2.5 Exclusion Criteria Related to Previous and Concomitant Treatments (Medications / non-medicinal therapies / procedures):

Ocular surgery or topical treatment concerned only eye undergoing CXL						
Before inclusion						After inclusion D1 to D5
At any time	**3 Years**	**1 Year**	**6 Months**	**1 Month**	**1 Week**	**Product period**
Corneal graft or corneal rings						
Corneal refractive surgery (e.g., LASIK, LASEK, PRK) or anticipated during the clinical investigation						
	Intravitreal injection					
		Previous corneal crosslinking				
			Systemic or topical calcineurin inhibitors (e.g. Restasis®, Ikervis®, pharmacy made formulations) or other non-steroidal immunosuppressive treatments			
			Amniotic membrane graft			
			Isotretinoïn			
			Other ocular surgery (e.g., palpebral and cataract surgery)			
			Permanent punctal plugs (with the exception of semi-permanent or temporary plugs with a prohibition period of 3 months)			
			Other laser procedures			
				Systemic or topical non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (except the standardised post-operative topical corticosteroid – *please refer to the investigator*		

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<tr><td></td><td>
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<tr><td colspan="5"></td><td colspan="2">*manual*)</td></tr>
<tr><td colspan="5"></td><td colspan="2">Any ophthalmic or systemic antibiotic treatment (except the standardised post-operative topical antibiotic – *please refer to the investigator manual*)</td></tr>
<tr><td colspan="5"></td><td colspan="2">Any anticipated changes of systemic medications that could affect a dry eye condition and healing process (e.g., antihistaminics, tricyclic antidepressants, anxiolytics, antimuscarinics, beta-blocking agents, phenothiazines, omega 3, oestrogen-progesterone or other oestrogen derivatives)</td></tr>
<tr><td colspan="5"></td><td colspan="2">Any change in eye lid hygiene</td></tr>
<tr><td colspan="5">Before inclusion</td><td colspan="2">After inclusion
D1 to D5</td></tr>
<tr><td>At any time</td><td>3 Years</td><td>1 Year</td><td>6 Months</td><td>1 Month</td><td>1 Week</td><td>Product period</td></tr>
<tr><td colspan="5"></td><td>Contact lens</td><td>Standardised bandage contact lens should be kept from D1 to D5 (*please refer to the investigator manual*)</td></tr>
<tr><td colspan="5"></td><td colspan="2">Any ophthalmic treatment other than authorised ones</td></tr>
<tr><td colspan="6"></td><td>Any Solution with silver salts, iodine or copper</td></tr>
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<tr><td></td><td>Patient should be instructed to refrain from administration of any chronic ophthalmic medication (except for investigational product and auxiliary products authorised by the clinical investigation plan).</td></tr>
<tr><td>Clinical visits and investigation duration</td><td>An individual patient's participation will involve 6 visits (screening, CXL [D1], post CXL at D2 (phone call), D3, D4 and D5) over up to a 65-day period.
Follow up of the patient can be extended if complete healing isn't reached, according to the investigator judgement.</td></tr>
<tr><td>Countries</td><td>Turkey, France, Spain, Morocco</td></tr>
<tr><td>Statistical Considerations</td><td>Analysis sets:
<u>Safety set</u>:
All enrolled patients, having received at least one dose of investigational product and considered as-treated.

<u>Intent-to-Treat (ITT) set</u>: All randomised patients having received at least one dose of the investigational product and considered as-randomised.

<u>Modified Intent-to-Treat set (mITT):</u></td></tr>
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	All randomised patients having received at least one dose of investigational product and with at least one post-baseline performance assessment on product. Per protocol (PP) set: All mITT patients without any major clinical investigation plan violation. Safety endpoints will be analysed in the safety set. Performance endpoints will be primarily analysed in the mITT set. **Baseline:** The baseline visit is the inclusion visit (D1) for all assessments. **Sample size:** The principal statistical hypothesis is the superiority of T4020 compared to control for the primary efficacy variable. The sample size determination is based on the primary efficacy endpoint, i.e. the response defined as complete healing of CED (absence of CED) in the eye undergoing CXL as assessed by the investigator on Corneal Fluorescein Staining (CFS) at slit lamp examination at Day 3 (D3) and Day 4 (D4) using the Hochberg procedure for multiple testing. Using this step-up procedure, unadjusted p-values are ordered from the largest (p1) to the smallest (p2). If the largest p-value (p1) is lower than 0.05, both null hypotheses can be rejected at the overall 5%-level of significance. If the largest p-value (p1) is greater than 0.05 and the smallest p-value (p2) lower than 0.025, only the null hypothesis corresponding to p2 can be rejected at the overall 5%-level of significance. Bases on estimated response rates of 60% in the T4020 group and 30% in the control group, 132 evaluable patients (66 per group) are needed to achieve at least 90% power using a two-sided 0.025 significant nominal level. **Interim analysis:** No interim analysis is planned.
Planned schedule	Planned initiation of the clinical investigation: September 2016 Planned completion date of the clinical investigation: June 2017

FLOW CHART: Clinical investigations are to be conducted as per the following schedule of investigation procedures:

Clinical investigation procedure	***Screening Within 60 Days [D] before D1***	***Visit D1***				***Visit D2= 24h (± 2h)*** [(a)]	***Visit D3 = 48h (± 2h)***	***Visit D4 = 72h (± 2h)***	***Final Visit D5 = 96h (± 2h)*** [(n)]
		Pre-op.	***Intra-op.***	***Post-op.***	***Phone call 4 hours post-op.*** [(a)]	***Phone call***			
Informed consent	X								
Demography / Smoking status	X								
Keratoconus (KC) history	X								
Ocular medical and surgical history	X								
Ocular surface disease index (OSDI)	X								X
Systemic medical and surgical history	X								
Verification of inclusion and exclusion criteria	X	X							
Previous and concomitant ocular/non ocular products	X	X				X	X	X	X
Patient diary :									
- Painkiller(s) use [(b)]		X[(c)]		X	X	X	X	X	X
- Ocular pain assessment (Numeric Rating Scale, NRS)	X[(c)]	X[(c)]		X	X [(d)]	X[(e)]	X[(e)]	X[(e)]	X[(e)]
Ocular symptoms [(f)]					X	X	X	X	X
Corneal topography with pachymetry	X								
Far Uncorrected and Best Corrected Visual acuity (UCVA and BCVA) with manifest refraction	X								X
Slit-lamp examination [(g)]	X	X					X	X	X
Tear Break-up time (TBUT) with fluorescein	X								
Corneal fluorescein staining with CED assessment and photos (blue light) [(h)]	X						X	X	X
Conjunctival staining with lissamine green	X								X
Conjunctival hyperaemia							X	X	X
Corneal sensitivity assessment (by the Cochet-Bonnet aesthesiometer)	X								
Peri-operative pachymetry			X						

Clinical investigation procedure	***Screening Within 60 Days [D] before D1***	***Visit D1***				***Visit D2= 24h (± 2h) [(a)]***	***Visit D3 = 48h (± 2h)***	***Visit D4 = 72h (± 2h)***	***Final Visit D5 = 96h (± 2h)[(o)]***
		Pre-op.	***Intra-op.***	***Post-op.***	***Phone call 4 hours post-op.[(a)]***	***Phone call***			
Intraocular pressure (IOP) measurement on both eyes (non-contact tonometry)	X								X[(i)]
Schirmer test with anaesthesia	X								
Surgery: epi-off corneal collagen cross-linking (CXL) procedure			X						
Randomisation		X							
Investigational product instillation			X[(j)]				X[(k)]		X[(l)]
Contact lens (CL) insertion [(m)]			X				X	X	
Peri-operative photos				X					
Urinary pregnancy test [(n)]	X								
Adverse Event(s) (AE) / Adverse Device Effect(s) (ADEs) collection		X	X	X	X	X	X	X	X

[(a)] A phone call will be performed 4 hours after the CXL procedure by the investigator/delegate to collect the ocular symptoms and to remind the patient to complete the diary. Visit D2 will be also a phone call done by the investigator/delegate.

[(b)] Number of painkiller(s) pills recorded by the patient in the patient diary will be collected. The 1st administration of the painkiller (Paracetamol 1g) will be done 1 hour after CXL. The 2nd administration will be at least 4 hours later and no more than 4 times daily. In case of real severe pain, patient can take Paracetamol 500mg with 30mg Codein instead of Paracetamol 1g, not exceeding 4 tablets/day (including tablets with paracetamol and tablets with paracetamol/codein).

[(c)] For training purposes.

[(d)] The patient should be instructed to note the NRS pain score 1 hour after CXL procedure before the 1st painkiller administration, then 3, 6 and 12 hours after CXL procedure and before painkiller administration.

[(e)] The patient should be instructed to note the NRS pain score at wake up time(8:00 am +/- 2h), midday (2:00 pm+/- 2h) and bedtime (8:00 pm +/- 2h) and before painkiller administration.

[(f)] Ocular symptoms (light sensitivity, burning/stinging, tearing, foreign body sensation) will be collected by the investigator/delegate.

[(g)] Slit lamp examination: any clinically relevant finding will be recorded.

[(h)] The CED will be measured with caliper / with the slit lamp after contact lens (CL) removal if applicable.

[(i)] IOP at visit D5 if complete healing.

[(j)] The investigational product will be instilled by the medical staff before CL insertion at the end of the CXL procedure at visit D1.

[(k)] The investigational product will be instilled by the medical staff after CL insertion at Visit D3.

[(l)] The investigational product will be instilled by the patient (on the CL) in the morning D5 before the Visit.

[(m)] The removal of the CL will be done with forceps after hydration before ocular examination and a new CL will be used at visit D3 and visit D4.

[(n)] Women of child bearing potential must have a negative urinary pregnancy test prior to the initial instillation of investigational product.

[(o)] Follow up of the patient can be done if complete healing isn't reached, according to the investigator judgement. All procedures will be performed as scheduled for the final visit D5.

Op.: Operatively