

## *Nicox Ordinary and Extraordinary General Meetings of April 14, 2021*

Sophia Antipolis, March 26, 2021

Dear Shareholder,

Today I am writing to you to request your continued support for Nicox by voting in our upcoming Ordinary and Extraordinary General Meetings convened on April 14, 2021.

2020 has been a year of great progress in our development programs. Despite the challenging circumstances due to the global COVID-19 pandemic, we initiated four late-stage clinical trials in 2020, including the ZERVIAE trial launched by our Chinese partner Ocumension Therapeutics, demonstrating the strength of our development teams, supported by very capable corporate and financial functions. Both of the pivotal Phase 3 efficacy trials for NCX 470 in glaucoma patients, Mont Blanc and Denali, are now underway, allowing for the potential submission for marketing approval in both the United States and China. Given the positive results of the Dolomites Phase 2 trial, and the fact that we selected the higher dose of NCX 470 in the initial adaptive design of the Mont Blanc trial, we eagerly await, as a first step, the Mont Blanc top-line results currently expected in the first half of next year.

As to NCX 4251, based on the encouraging data from the Danube Phase 2 trial in blepharitis patients, we also now have a larger Phase 2b trial, Mississippi, up and running, with top-line results currently expected before the end of this year. Depending on those results, it may be that we only need one further pivotal trial to be able to submit NCX 4251 for approval in the United States.

Alongside the launch of ZERVIAE in the United States by our partner EyeVance Pharmaceuticals, recently acquired by the Japanese company, Santen, we have continued to expand our portfolio of licensees for this product in the rest of the world. Our partner Bausch + Lomb has also widened the availability of VYZULTA in the U.S. market by increasing its insurance coverage; and as a consequence VYZULTA prescriptions have increased despite the restrictions caused by the COVID-19 pandemic. Beyond the U.S and Canada, VYZULTA has been launched in Mexico, Argentina and Hong Kong and is approved or under regulatory review in many other countries.

We were grateful for the strong support from investors in our December equity financing and in the restructuring of our bond financing agreement with Kreos Capital, which ensure Nicox remains financed beyond the key upcoming Mississippi and Mont Blanc results.

This means we can retain our focus on execution of the ongoing clinical trials throughout 2021, aiming to keep them on track to deliver results according to our expected timelines. In addition, we expect to continued growth in our licensing revenues as prescriptions increase for VYZULTA and ZERVIAE. In short, we believe the right team and assets are in place to position the company for growth as a leading player in ophthalmology.

Your support and your vote in the upcoming Ordinary and Extraordinary General Meetings are very important to us being able to build on our past successes and continue to achieve our objectives.

For this purpose, a proxy form, the resolutions, a guide explaining how to vote, and several other documents pertaining to the General Meetings are enclosed. All the documents pertaining to the General Meetings are available on Nicox's website [www.nicox.com](http://www.nicox.com) ('Shareholder Meetings' button on the home page).

Should you have any question on the voting process, please contact our Investor Relations team either by e-mail at [age2021nicox@nicox.com](mailto:age2021nicox@nicox.com) or by phone at 04 97 24 53 28.

With my best regards,

MICHELE GARUFI

Chairman & Chief Executive Officer

Important : Avant d'exercer votre choix, veuillez prendre connaissance des instructions situées au verso - Important : Before selecting please refer to instructions on reverse side  
Quelle que soit l'option choisie, noircir comme ceci ■ la ou les cases correspondantes, dater et signer au bas du formulaire - Whichever option is used, shade box(es) like this ■, date and sign at the bottom of the form

☐ JE DÉSIRE ASSISTER À CETTE ASSEMBLÉE et demande une carte d'admission : dater et signer au bas du formulaire / I WISH TO ATTEND THE SHAREHOLDER'S MEETING and request an admission card: date and sign at the bottom of the form

NICOX SA  
DRAKKAR D - 2405 ROUTE DES DOLINES  
06560 VALBONNE SOPHIA ANTIPOLIS

Au Capital de 37 103 985 EUR  
403 942 642 R.C.S. GRASSE

ASSEMBLEES GENERALES ORDINAIRE ET  
EXTRAORDINAIRE  
Du Mercredi 14 Avril 2021 à 14H00  
ORDINARY AND EXTRAORDINARY GENERAL  
MEETINGS  
On Wednesday the 14th of April 2021 at 2.00 pm

CADRE RÉSERVÉ À LA SOCIÉTÉ - FOR COMPANY'S USE ONLY

Identifiant - Account		
Nombre d'actions Number of shares	Nominatif Registered	Vote simple Single vote
	Porteur Bearer	Vote double Double vote
Nombre de voix - Number of voting rights		

<input type="checkbox"/> JE VOTE PAR CORRESPONDANCE / I VOTE BY POST Cf. au verso (2) - See reverse (2)										Sur les projets de résolutions non agréés, je vote en noircissant la case correspondant à mon choix. On the draft resolutions not approved, I cast my vote by shading the box of my choice.	
AG ORDINAIRE					AG EXTRAORDINAIRE					AGO	AGE
1	2	3	4	5	1	2	3	4	5	A	A
Non / No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Oui / Yes	<input type="checkbox"/>
Abs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Non / No	<input type="checkbox"/>
6	7	8	9	10	6	7	8	9	10	B	B
Non / No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Oui / Yes	<input type="checkbox"/>
Abs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Non / No	<input type="checkbox"/>
11	12	13	14		11	12	13			C	C
Non / No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Oui / Yes	<input type="checkbox"/>
Abs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Non / No	<input type="checkbox"/>
										Abs.	<input type="checkbox"/>
										D	D
Non / No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Oui / Yes	<input type="checkbox"/>
Abs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Non / No	<input type="checkbox"/>
										Abs.	<input type="checkbox"/>
										E	E
Non / No	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Oui / Yes	<input type="checkbox"/>
Abs.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Non / No	<input type="checkbox"/>
										Abs.	<input type="checkbox"/>

Si des amendements ou des résolutions nouvelles étaient présentés en assemblée, je vote NON sauf si je signale un autre choix en noircissant la case correspondante :  
In case amendments or new resolutions are proposed during the meeting, I vote NO unless I indicate another choice by shading the corresponding box:

- Je donne pouvoir au Président de l'assemblée générale. / I appoint the Chairman of the general meeting..... ☐

- Je m'abstiens. / I abstain from voting ..... ☐

- Je donne procuration [cf. au verso renvoi (4)] à M., Mme ou Mlle, Raison Sociale pour voter en mon nom ..... ☐

I appoint [see reverse (4)] Mr, Mrs or Miss, Corporate Name to vote on my behalf..... ☐

Pour être pris en considération, tout formulaire doit parvenir au plus tard :  
To be considered, this completed form must be returned no later than:

à la banque / to the bank 11/04/2021

Date & Signature

« Si le formulaire est renvoyé daté et signé mais qu'aucun choix n'est coché (carte d'admission / vote par correspondance / pouvoir au président / pouvoir à mandataire), cela vaut automatiquement pouvoir au Président de l'assemblée générale »  
If the form is returned dated and signed but no choice is checked (admission card / postal vote / power of attorney to the President / power of attorney to a representative), this automatically applies as a proxy to the Chairman of the General Meeting

## CONDITIONS D'UTILISATION DU FORMULAIRE

<p><b>(1) GENERALITES : Il s'agit d'un formulaire unique prévu par l'article R. 225-76 du Code de Commerce. QUELLE QUE SOIT L'OPTION CHOISIE :</b></p> <p>Le signataire est prié d'inscrire très exactement, dans la zone réservée à cet effet, ses nom (en majuscules), prénom usuel et adresse (les modifications de ces informations doivent être adressées à l'établissement concerné et ne peuvent être effectuées à l'aide de ce formulaire).</p> <p>Pour les personnes morales, le signataire doit renseigner ses nom, prénom et qualité.</p> <p>Si le signataire n'est pas l'actionnaire (exemple : Administrateur légal, Tuteur, etc.) il doit mentionner ses nom, prénom et la qualité en laquelle il signe le formulaire de vote.</p> <p>Le formulaire adressé pour une assemblée vaut pour les assemblées successives convoquées avec le même ordre du jour (article R. 225-77 alinéa 3 du Code de Commerce).</p> <p>Le texte des résolutions figure dans le dossier de convocation joint au présent formulaire (article R. 225-81 du Code de Commerce). Ne pas utiliser à la fois « Je vote par correspondance » et « Je donne pouvoir » (article R. 225-81 paragraphe 8 du Code de Commerce).</p> <p>Un guide méthodologique de traitement des assemblées générales, incluant une grille de lecture de ce formulaire de vote par correspondance est disponible sur le site de l'AFTI : <a href="http://www.afti.asso.fr">www.afti.asso.fr</a></p> <p><b>La version française de ce document fait foi.</b></p>	<p><b>(3) POUVOIR AU PRÉSIDENT DE L'ASSEMBLÉE GÉNÉRALE</b> <u>Article L. 225-106 du Code de Commerce (extraît) :</u></p> <p>"Pour toute procuration d'un actionnaire sans indication de mandataire, le président de l'assemblée générale émet un vote favorable à l'adoption de projets de résolutions présentés ou agréés par le conseil d'administration ou le directoire, selon le cas, et un vote défavorable à l'adoption de tous les autres projets de résolution. Pour émettre tout autre vote, l'actionnaire doit faire choix d'un mandataire qui accepte de voter dans le sens indiqué par le mandant".</p>	<p>Cette information porte notamment sur le fait que le mandataire ou, le cas échéant, la personne pour le compte de laquelle il agit :</p> <p>1° Contrôle, au sens de l'article L. 233-3, la société dont l'assemblée est appelée à se réunir ;</p> <p>2° Est membre de l'organe de gestion, d'administration ou de surveillance de cette société ou d'une personne qui la contrôle au sens de l'article L. 233-3 ;</p> <p>3° Est employé par cette société ou par une personne qui la contrôle au sens de l'article L. 233-3 ;</p> <p>4° Est contrôlé ou exerce l'une des fonctions mentionnées au 2° ou au 3° dans une personne ou une entité contrôlée par une personne qui contrôle la société, au sens de l'article L. 233-3.</p>
<p><b>(2) VOTE PAR CORRESPONDANCE</b> <u>Article L. 225-107 du Code de Commerce (extraît) :</u></p> <p>"Tout actionnaire peut voter par correspondance, au moyen d'un formulaire dont les mentions sont fixées par décret en Conseil d'Etat. Les dispositions contraires des statuts sont réputées non écrites.</p> <p>Pour le calcul du quorum, il n'est tenu compte que des formulaires qui ont été reçus par la société avant la réunion de l'assemblée, dans les conditions de délais fixées par décret en Conseil d'Etat. Les formulaires ne donnant aucun sens de vote ou exprimant une abstention ne sont pas considérés comme des votes exprimés".</p> <p>La majorité requise pour l'adoption des décisions est déterminée en fonction des voix exprimées par les actionnaires présents ou représentés. Les voix exprimées ne comprennent pas celles attachées aux actions pour lesquelles l'actionnaire n'a pas pris part au vote, s'est abstenu ou a voté blanc ou nul. (articles L. 225-96 et L. 225-98 du Code de Commerce et, s'agissant des sociétés ayant adopté le statut de la société européenne, et articles 57 et 58 du Règlement du Conseil (CE) N°2157/2001 relatif au statut de la société européenne).</p> <p>Si vous votez par correspondance : vous devez obligatoirement noircir la case "Je vote par correspondance" au recto.</p> <p>1 - il vous est demandé pour chaque résolution en noirissant individuellement les cases correspondantes :</p> <ul style="list-style-type: none"><li>- soit de voter "Oui" (vote exprimé par défaut pour les projets de résolutions présentés ou agréés, en l'absence d'un autre choix);</li><li>- soit de voter "Non";</li><li>- soit de vous "Abstenir" en noirissant individuellement les cases correspondantes.</li></ul> <p>2 - Pour le cas où des amendements aux résolutions présentées ou des résolutions nouvelles seraient déposées lors de l'assemblée, il vous est demandé d'opter entre vote contre (vote exprimé par défaut en l'absence d'un autre choix), pouvoir au président de l'assemblée générale, abstention ou pouvoir à personne dénommée en noirissant la case correspondant à votre choix.</p>	<p><b>(4) POUVOIR À UNE PERSONNE DÉNOMMÉE</b> <u>Article L. 225-106 du Code de Commerce (extraît) :</u></p> <p>"I - Un actionnaire peut se faire représenter par un autre actionnaire, par son conjoint ou par le partenaire avec lequel il a conclu un pacte civil de solidarité.</p> <p>II - Le mandat ainsi que, le cas échéant, sa révocation sont écrits et communiqués à la société. Les conditions d'application du présent alinéa sont précisées par décret en Conseil d'Etat.</p> <p>III - Avant chaque réunion de l'assemblée générale des actionnaires, le président du conseil d'administration ou le directoire, selon le cas, peut organiser la consultation des actionnaires mentionnés à l'article L. 225-102 afin de leur permettre de désigner un ou plusieurs mandataires pour les représenter à l'assemblée générale conformément aux dispositions du présent article.</p> <p>Cette consultation est obligatoire lorsque, les statuts ayant été modifiés en application de l'article L. 225-23 ou de l'article L. 225-71, l'assemblée générale ordinaire doit nommer au conseil d'administration ou au conseil de surveillance, selon le cas, un ou des salariés actionnaires ou membres des conseils de surveillance des fonds communs de placement d'entreprise détenant des actions de la société. Cette consultation est également obligatoire lorsque l'assemblée générale extraordinaire doit se prononcer sur une modification des statuts en application de l'article L. 225-23 ou de l'article L. 225-71.</p> <p>Les clauses contraires aux dispositions des alinéas précédents sont réputées non écrites."</p>	<p>Cette information est également délivrée lorsqu'il existe un lien familial entre le mandataire ou, le cas échéant, la personne pour le compte de laquelle il agit, et une personne physique placée dans l'une des situations énumérées aux 1° à 4°.</p> <p>Lorsqu'en cours de mandat, survient l'un des faits mentionnés aux alinéas précédents, le mandataire en informe sans délai son mandant. A défaut par ce dernier de confirmation expresse du mandat, celui-ci est caduc.</p> <p>La caducité du mandat est notifiée sans délai par le mandataire à la société.</p> <p>Les conditions d'application du présent article sont précisées par décret en Conseil d'Etat."</p>
<p>Les informations à caractère personnel recueillies dans le cadre du présent document sont nécessaires à l'exécution de vos instructions de vote. Vous disposez d'un certain nombre de droits concernant vos données (accès, rectification, etc.). Ces droits peuvent être exercés auprès de votre teneur de compte aux coordonnées indiquées par ce dernier.</p>		

## FORM TERMS AND CONDITIONS

<p><b>(1) GENERAL INFORMATION: This is the sole form pursuant to article R. 225-76 du Code de Commerce WHICHEVER OPTION IS USED:</b></p> <p>The signatory should write his/her exact name and address in capital letters in the space provided e.g. a legal guardian: (Change regarding this information have to be notified to relevant institution, no change can be made using this proxy form).</p> <p>If the signatory is a legal entity, the signatory should indicate his/her full name and the capacity in which he is entitled to sign on the legal entity's behalf.</p> <p>If the signatory is not the shareholder (e.g. a legal guardian), please specify your full name and the capacity in which you are signing the proxy.</p> <p>The form sent for one meeting will be valid for all meetings subsequently convened with the same agenda (art. R. 225-77 alinéa 3 du Code de Commerce).</p> <p>The text of the resolutions is in the notification of the meeting which is sent with this proxy (article R. 225-81 du Code de Commerce). Please do not use both "I vote by post" and "I hereby appoint" (article R. 225-81 du Code de Commerce).</p> <p>A guide relating to the general meetings processing, including an interpretation grid of this proxy form, is available on the AFTI website at: <a href="http://www.afti.asso.fr">www.afti.asso.fr</a></p> <p><b>The French version of this document governs; The English translation is for convenience only.</b></p>	<p><b>(3) PROXY TO THE CHAIRMAN OF THE GENERAL MEETING</b> <u>Article L. 225-106 du Code de Commerce (extract):</u></p> <p>"In case of any power of representation given by a shareholder without naming a proxy, the chairman of the general meeting shall issue a vote in favor of adopting a draft resolutions submitted or approved by the Board of Directors or the Management Board, as the case may be, and a vote against adopting any other draft resolutions. To issue any other vote, the shareholder must appoint a proxy who agrees to vote in the manner indicated by his principal."</p>	<p>This information relates in particular to the event that the proxy or, as the case may be, the person on behalf of whom it acts:</p> <p>1° Controls, within the meaning of article L. 233-3, the company whose general meeting has to meet;</p> <p>2° Is member of the management board, administration or supervisory board of the company or a person which controls it within the meaning of the article L. 233-3;</p> <p>3° Is employed by the company or a person which controls it within the meaning of article L. 233-3;</p> <p>4° Is controlled or carries out one of the functions mentioned with the 2° or the 3° in a person or an entity controlled by a person who controls the company, within the meaning of the article L. 233-3.</p>
<p><b>(2) POSTAL VOTING FORM</b> <u>Article L. 225-107 du Code de Commerce (extract):</u></p> <p>"Any shareholder may vote by post, using a form the wording of which shall be fixed by a decree approved by the Conseil d'Etat. Any provisions to the contrary contained in the memorandum and articles of association shall be deemed non-existent.</p> <p>When calculating the quorum, only forms received by the company before the meeting shall be taken into account, on conditions to be laid down by a decree approved by the Conseil d'Etat. The forms giving no voting direction or indicating abstention shall not be considered as votes cast."</p> <p>The majority required for the adoption of the general meeting's decisions shall be determined on the basis of the votes cast by the shareholders present or represented. The votes cast shall not include votes attaching to shares in respect of which the shareholder has not taken part in the vote or has abstained or has returned a blank or spoilt ballot paper (articles L. 225-96 and L. 225-98 du Code de Commerce and, for the companies which have adopted the statute of European company, articles 57 and 58 of the Council Regulation (EC) n°2157/2001 on the statute for a European company).</p> <p>If you wish to use the postal voting form, you have to shade the box on the front of the document: "I vote by post".</p> <p>1 - In such event, please comply for each resolution the following instructions by shading boxes of your choice:</p> <ul style="list-style-type: none"><li>- either vote "Yes" (in absence of choice, vote expressed by default for the approved draft resolutions),</li><li>- or vote "No",</li><li>- or vote "Abstention" by shading boxes of your choice.</li></ul> <p>2 - In case of amendments or new resolutions during the general meeting, you are requested to choose between vote "No" (vote expressed by default in absence of choice), proxy to the chairman of the general meeting, "Abstention" or proxy to a mentioned person individual or legal entity by shading the appropriate box.</p>	<p><b>(4) PROXY TO A MENTIONED PERSON (INDIVIDUAL OR LEGAL ENTITY)</b> <u>Article L. 225-106 du Code de Commerce (extract):</u></p> <p>"I - A shareholder may be represented by another shareholder, by his or her spouse, or by his or her partner who he or she has entered into a civil union with.</p> <p>II - The proxy as well as its dismissal, as the case may be, must be written and made known to the company. A Conseil d'Etat decree specifies the implementation of the present paragraph.</p> <p>III - Before every general meeting, the chairman of the board of directors or the management board, as the case may be, may organise a consultation with the shareholders mentioned in article L. 225-102 to enable them to appoint one or more proxies to represent them at the meeting in accordance with the provisions of this Article.</p> <p>Such a consultation shall be obligatory where, following the amendment of the memorandum and articles of association pursuant to article L. 225-23 or article L. 225-71, the ordinary general meeting is required to appoint to the board of directors or the supervisory board, as the case may be, one or more shareholder employees or members of the supervisory board of the company investment funds that holds company's shares. Such a consultation shall also be obligatory where a special shareholders' meeting is required to take a decision on an amendment to the memorandum and articles of association pursuant to article L. 225-23 or article L. 225-71.</p> <p>Any clauses that conflict with the provisions of the preceding sub-paragraphs shall be deemed non-existent."</p>	<p>This information is also delivered when a family tie exists between the proxy or, as the case may be, the person on behalf of whom it acts, and a natural person placed in one of the situations enumerated from 1° to 4° above.</p> <p>When during the proxy, one of the events mentioned in the preceding subparagraphs occurs, the proxy informs without delay his constituent. Failing by the latter to confirm explicitly the proxy, this one is null and void.</p> <p>The termination of the proxy is notified without delay by the proxy to the company.</p> <p>The conditions of application of this article are determined by a Conseil d'Etat decree."</p>
<p><u>Article L. 22-10-41 du Code de commerce:</u></p> <p>"Any person who proceeds to an active request of proxy, while proposing directly or indirectly to one or more shareholders, under any form and by any means, to receive proxy to represent them at the general meeting of a company mentioned in the first paragraph of the article L. 22-10-39, shall release its voting policy.</p> <p>It can also release its voting intentions on the draft resolutions submitted to the general meeting. It exercises then, for any proxy received without voting instructions, a vote in conformity with the released voting intentions. The conditions of application of this article are determined by a Conseil d'Etat decree."</p>		
<p><u>Article L. 22-10-42 du Code de commerce:</u></p> <p>"The commercial court of which the company's head office falls under can, at the request of the constituent and for a duration which cannot exceed three years, deprive the proxy of the right to take part in this capacity to any general meeting of the relevant company in the event of non-compliance with mandatory information envisaged from the third to seventh paragraphs of article L. 22-10-40 or with the provisions of article L. 22-10-41. The court can decide the publication of this decision at the expenses of the proxy.</p> <p>The court can impose the same sanctions towards the proxy on request of the company in the event of non-compliance of the provisions of the article L. 22-10-41."</p>		
<p>Personal data included in this form are necessary for the execution of your voting instructions. You have certain minimum rights regarding your data (access, correction...). These rights may be exercised using the contact details provided by your custodian.</p>		



## How to participate in the shareholder meetings

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All Nicox shareholders are entitled to take part in the shareholder meetings. You may:

- attend the shareholder meetings in person,
- be represented by any person or legal entity,
- give power of attorney to the Chairman,
- vote by correspondence.

**In the current context of the Covid 19 pandemic, shareholders are invited to vote by correspondence or by internet, through the website VOTACCESS or to give proxy to the Company.** The arrangements for physical participation in the shareholder meetings could be subject to modification. Shareholders are invited to regularly consult the section dedicated to the 2021 shareholder meetings on the Company's website [www.nicox.com](http://www.nicox.com).

These options are offered to you both in the attached proxy form and in a dedicated internet platform, as explained hereafter.

We are available to help you should you have any additional question regarding the shareholder meetings:

- Nicox's Investor Relations: [age2021nicox@nicox.com](mailto:age2021nicox@nicox.com) or +33 (0) 4 97 24 53 28

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**If your shares are in REGISTERED form, please fill in the proxy form as explained below and send it in the prepaid return envelope sent with your personal notice of convening if you live in France (or by post to Société Générale Securities Services - Service Assemblée Générale - 32 rue du Champ de Tir - CS 30812 - 44312 NANTES Cedex 3 if you live abroad).**

**If your shares are in BEARER form, please fill in the proxy form as explained below and send it to the financial institution holding the shares who will in turn send it, with a share certificate to Société Générale Securities Services - Service Assemblée Générale - 32 rue du Champ de Tir - CS 30812 - 44312 NANTES Cedex 3.**

**IF YOUR SHARES ARE IN BEARER FORM, A SHARE CERTIFICATE ISSUED BY YOUR BANK MENTIONING THE SHAREHOLDER MEETINGS OF APRIL 14, 2021, MUST ACCOMPANY YOUR PROXY FORM.**

The proxy form (together with the share certificate if your shares are in bearer form) must be received on or before April 11, 2021 (or April 25, 2021, on second call if the quorum is not reached) by Société Générale Securities Services - Service Assemblée Générale - 32 rue du Champ de Tir - CS 30812 - 44312 NANTES Cedex 3.

### 1. How to participate using the enclosed proxy form

Please send back this proxy form to your bank, completed as explained below.

#### 1.1. If you wish to attend the shareholder meetings in person

- Tick the corresponding box of the proxy form.
- Add your name and address or check that they are correct if they are already included.
- Date and sign the proxy form.
- Send back the proxy form to your bank (for the holders of bearer shares) or to Société Générale (if you hold registered shares).

You will receive an admission card\*.

\* If you have not received your admission card in the 2 days preceding the shareholders meetings, please contact us at [age2021nicox@nicox.com](mailto:age2021nicox@nicox.com).

## 1.2. If you wish to vote without attending the shareholder meetings in person

TO GIVE PROXY TO THE CHAIRMAN	TO VOTE BY CORRESPONDENCE	TO GIVE PROXY TO ANY PERSON OR LEGAL ENTITY
<ul style="list-style-type: none"><li>• Tick box <b>2</b> of the proxy form.</li><li>• Add your name and address or check that they are correct if they are already included.</li><li>• Date and sign the proxy form.</li><li>• Send back the proxy form to your bank who will send it in turn to Société Générale (with the share certificate if necessary) <b><u>by April 11, 2021 (or April 25, 2021 on second call)</u></b>.</li></ul> <p>Your vote will follow the Chairman's vote.</p> <p><b>You have voted.</b></p>	<ul style="list-style-type: none"><li>• Tick box <b>1</b> of the proxy form.</li><li>• Fill in the box on the left to indicate your vote for each resolution (darkening the little box in front of each resolution number means voting against the resolution or abstention from voting).</li><li>• Do not darken the little box if you wish to vote 'in favor' of a resolution.</li><li>• Add your name and address or check that they are correct if they are already included.</li><li>• Date and sign the proxy form.</li><li>• Send back the proxy form to your bank who will send it in turn to Société Générale (with the share certificate if necessary) <b><u>by April 11, 2021 (or April 25, 2021 on second call)</u></b>.</li></ul> <p><b>You have voted.</b></p>	<ul style="list-style-type: none"><li>• Tick box <b>3</b> of the proxy form.</li><li>• Add the identity and contact details of the person or legal entity that will represent you.</li><li>• Add your name and address or check that they are correct if they are already included.</li><li>• Date and sign the proxy form.</li><li>• Send back the proxy form to your bank who will send it in turn to Société Générale (with the share certificate if necessary) <b><u>by April 11, 2021 (or April 25, 2021 on second call)</u></b>.</li></ul> <p><b>You have given proxy.</b></p>

**The proxy form (together with the share certificate if your shares are in bearer form) must be received on or before April 11, 2021 (or April 25, 2021, on second call if the quorum is not reached) by Société Générale Securities Services - Service Assemblée Générale - 32 rue du Champ de Tir - CS 30812 - 44312 NANTES Cedex 3**

### 1.3. How to fill in your proxy form

TO ATTEND THE MEETING IN PERSON

Avant d'exercer votre choix, veuillez soit l'option choisie, noircir comme ci

☐ JE DÉSIRE ASSISTER À CETTE ASSEMBLÉE

TO VOTE BY CORRESPONDENCE  
Tick box 1  
Then vote as per the instructions

TO GIVE PROXY TO THE CHAIRMAN

Tick box 2

TO GIVE PROXY TO ANY PERSON OR LEGAL ENTITY

Tick box 3

**NICOX SA**  
DRAKKAR D - 2405 ROUTE DES DOLINES  
06560 VALBONNE SOPHIA ANTIPOLIS

Au Capital de 37 103 985 EUR  
403 942 642 R.C.S. GRASSE

**ASSEMBLÉES GÉNÉRALES ORDINAIRE ET EXTRAORDINAIRE**  
Du Mercredi 14 Avril 2021 à 14H00

**ORDINARY AND EXTRAORDINARY GENERAL MEETINGS**  
On Wednesday the 14th of April 2021 at 2.00 pm

**CADRE RÉSERVÉ À LA SOCIÉTÉ - FOR COMPANY'S USE ONLY**

Identifiant - Account

Nombre d'actions / Number of shares

Porteur / Bearer

Vote simple / Single vote

Vote double / Double vote

Nombre de voix - Number of voting rights

<b>1 JE VOTE PAR CORRESPONDANCE / I VOTE BY POST</b> Cf. au verso (2) - See reverse (2) Je vote OUI à tous les projets de résolutions présentés ou agréés par le Conseil d'Administration ou le Directoire ou la Gérance, à l'EXCEPTION de ceux que je signale en noircissant comme ceci l'une des cases "Non" ou "Abstention". / I vote YES all the draft resolutions approved by the Board of Directors, EXCEPT those indicated by a shaded box, like this, for which I vote No or I abstain.										<b>2 JE DONNE POUVOIR AU PRÉSIDENT DE L'ASSEMBLÉE GÉNÉRALE</b> Cf. au verso (3) I HEREBY GIVE MY PROXY TO THE CHAIRMAN OF THE GENERAL MEETING See reverse (3)										<b>3 JE DONNE POUVOIR À :</b> Cf. au verso (4) pour me représenter à l'Assemblée / to represent me at the above mentioned Meeting M. Mme ou Mlle, Raison Sociale / Mr, Mrs or Miss, Corporate Name Adresse / Address									
AG ORDINAIRE					AG EXTRAORDINAIRE					AGO		AGE																	
1	2	3	4	5	1	2	3	4	5	A	A																		
Non / No										Oui / Yes																			
Abs.										Non / No																			
										Abs.																			
6	7	8	9	10	6	7	8	9	10	B	B																		
Non / No										Oui / Yes																			
Abs.										Non / No																			
										Abs.																			
11	12	13	14		11	12	13			C	C																		
Non / No										Oui / Yes																			
Abs.										Non / No																			
										Abs.																			
Non / No										D	D																		
Abs.										Oui / Yes																			
										Non / No																			
										Abs.																			
Non / No										E	E																		
Abs.										Oui / Yes																			
										Non / No																			
										Abs.																			

Si des amendements ou des résolutions nouvelles étaient présentés en assemblée, je vote NON sauf si je signale un autre choix en noircissant la case correspondante :  
 In case amendments or new resolutions are proposed during the meeting, I vote NO unless I indicate another choice by shading the corresponding box:

- Je donne pouvoir au Président de l'assemblée générale. / I appoint the Chairman of the general meeting

- Je m'abstiens. / I abstain from voting

- Je donne procuration [cf. au verso renvoi (4)] à M., Mme ou Mlle, Raison Sociale pour voter en mon nom / I appoint [see reverse (4)] Mr, Mrs or Miss, Corporate Name to vote on my behalf

Pour être pris en considération, tout formulaire doit parvenir au plus tard :  
 To be considered, this completed form must be returned no later than:

à la banque / to the bank 11/04/2021

Date & Signature

Add your name and address or check that they are correct if they are already included (whatever your choice is)

DATE and SIGN here (whatever your choice is)

- Si le formulaire est renvoyé daté et signé mais qu'aucun choix n'est coché (carte d'admission / vote par correspondance / pouvoir au président / pouvoir à mandataire), cela vaut automatiquement pouvoir au Président de l'assemblée générale -  
 If the form is returned dated and signed but no choice is checked (admission card / postal vote / power of attorney to the President / power of attorney to a representative), this automatically applies as a proxy to the Chairman of the General Meeting

## **2. How to participate in the shareholder meetings via Internet platform Votaccess**

Nicox has set up a dedicated on-line voting website ahead of the shareholder meetings, as explained below.

**Votaccess will be open from March 26, 2021 at 9:00 am until April 13, 2021 at 3:00 pm (CET) (and from April 15, 2021 at 9:00 am until April 27, 2021 at 3:00 pm (CET) in case of second call). To avoid overloading the site, we recommend that you do not wait until the last day to vote.**

### **2.1 Attend the shareholder meetings in person**

#### **Registered shares**

If you hold registered shares, you should log onto the secure website [www.sharinbox.societegenerale.com](http://www.sharinbox.societegenerale.com) by entering the identification numbers sent to you by post when you were first in contact with Société Générale Securities Services. On the home page, click on the name of the meeting in the "Current Operation" menu. Select the operation, follow the instruction and click on the "Vote" button to access the voting website.

#### **Bearer shares**

If you hold bearer shares you should log onto the web portal of your bank or broker, with your usual user name and password, to connect to the VOTACCESS site and vote. You simply click on the icon displayed on the line corresponding to your Nicox shares. You will only be able to connect in this way if your bank or broker is a member of the VOTACCESS system.

### **2.2 Vote through Internet**

#### **Registered shares**

If you hold registered shares, you should log onto the secure website [www.sharinbox.societegenerale.com](http://www.sharinbox.societegenerale.com) by entering the identification numbers sent to you by post when you were first in contact with Société Générale Securities Services. On the home page, click on the name of the meeting in the "Current Operation" menu. Select the operation, follow the instruction and click on the "Vote" button to access the voting website.

#### **Bearer shares**

If you hold bearer shares you should log onto the web portal of your bank or broker, with your usual user name and password, to connect to the VOTACCESS site and vote. You simply click on the icon displayed on the line corresponding to your Nicox shares. You will only be able to vote in this way if your bank or broker is a member of the VOTACCESS system.

### **2.3 Give proxy to the Chairman or to any other person of your choice through internet**

In accordance with Article R. 225-79 of the French Commercial Code, you may give proxy or withdraw a proxy (to the chairman of the meeting or to any other person) electronically by logging onto the website [www.sharinbox.societegenerale.com](http://www.sharinbox.societegenerale.com) if you hold registered shares, or onto the website of your bank or broker if you hold bearer shares, with your usual username and password, in order to connect to the VOTACCESS site as described above.

If your bank or broker is not a member of the VOTACCESS system, the notification of the designation or revocation of a proxy can be done electronically up to the day before the shareholder meetings at 3pm CET (up to April 13, 2021 at 3 pm or up to April 27, 2021 at 3 pm in case of second call) by sending an email find electronically through an accredited certification service provider in accordance with applicable laws and regulations to [age2021nicox@nicox.com](mailto:age2021nicox@nicox.com) including the following information: name, first name, address and bank details as well as the name and first name of the designated or revoked proxy. The shareholder must request his bank or broker to send a confirmation to Nicox SA; - Drakkar D, 2405 routes de Dolines – 05650 Valbonne – France.

If you give proxy to the Chairman, he will vote in favor of all of the resolutions presented or supported by the Board of Directors and against all resolutions not supported by the Board.

**NICOX SA**

**AGENDA AND SUMMARY OF THE DRAFT RESOLUTIONS**

**ORDINARY SHAREHOLDER MEETING  
FOLLOWED BY AN EXTRAORDINARY SHAREHOLDER MEETING**

**CONVENED ON APRIL 14, 2021**  
**(AND ON SECOND CALL ON APRIL 28, 2021)**

*Agenda of the ordinary shareholder meeting*

- Approval of the 2020 annual statutory accounts (resolution 1).
- Allocation of the 2020 year-end results (resolution 2).
- Approval of the 2020 consolidated accounts (resolution 3).
- Statutory Auditors' report on agreements with related parties (resolution 4).
- Authorization for the Board of Directors to purchase Company's shares (resolution 5).
- Approval of the information on the remuneration of the directors and corporate officers included in the corporate governance report pursuant to Article L. 22-10-9 of the French Commercial Code (resolution 6).
- Approval of the components of the remuneration paid or granted to Michele Garufi, Chairman and CEO, in respect of fiscal year 2020 (resolution 7).
- Approval of the remuneration policy of the directors and corporate officers (resolution 8).
- Decision on the amount of the annual remuneration of the Board members (resolution 9).
- Renewal of the term of office of Michele Garufi, Board member (resolution 10).
- Renewal of the term of office of Luzi von Bidder, Board member (resolution 11).
- Renewal of the term of office of Ms. Adrienne Graves, Board member (resolution 12).
- Renewal of the term of office of MS. Lauren Silvernail, Board member (resolution 13).
- Power of attorney to complete the formalities (resolution 14).

*Agenda of the extraordinary meeting*

- Delegation of competence to the Board of Directors to issue shares, equity securities giving right to other equity securities or debt securities and other securities giving access to newly issued equity securities of the Company, with preferential right of subscription of the shareholders (resolution 1).
- Delegation of competence to the Board of Directors to issue shares, equity securities giving right to other equity securities or debt securities and other securities giving access to newly issued equity securities, without preferential right of subscription of the shareholders and



by way of public offering (other than the public offering pursuant to Article L. 411-2 1° of the French Financial and Monetary Code) (resolution 2).

Delegation of competence to the Board of Directors to issue shares, equity securities giving right to other equity securities or debt securities and other securities giving access to newly issued equity securities, without preferential right of subscription of the shareholders and by way of a public offering pursuant to Article L 411-2 1° of the French Financial and Monetary Code (private placement) (resolution 3).

- Authorization to the Board of Directors to set the issue price of securities to be issued in the context of an issuance carried out pursuant to the second and third resolutions within the limit of 10% of the share capital (resolution 4).
- Authorization to the Board of Directors to increase the number of securities to be issued in the context of an issuance carried out pursuant to the first, second, third, fourth and eighth resolutions, with or without preferential right of subscription of the shareholders (resolution 5).
- Delegation of competence to the Board of Directors to increase the share capital by capitalization of reserves, provisions, premiums or other sums the capitalization of which would be permitted (resolution 6).
- Delegation of powers to the Board of Directors to increase the share capital in consideration for capital contributions in kind out of the scope of a public exchange offer, within the limit of 10% of the share capital (resolution 7).
- Delegation of competence to the Board of Directors to increase the share capital for the benefit of a category of investors without preferential right of subscription of the shareholders (resolution 8).
- Delegation of competence to the Board of Directors to increase the share capital in connection with a profit sharing plan reserved for the Company's employees without preferential right of subscription of the shareholders (resolution 9).
- Authorization to the Board of Directors to grant free shares, existing or to be issued, without preferential right of subscription of the shareholders (resolution 10).
- Authorization to the Board of Directors to grant stock-options to subscribe new shares or purchase existing shares without preferential right of subscription of the shareholders (resolution 11).
- Authorization to the Board of Directors to reduce the share capital by cancellation of previously repurchased shares in the context of a share repurchase plan (resolution 12).
- Power of attorney to complete the formalities (resolution 13).

## **SUMMARY OF THE RESOLUTIONS ORDINARY SHAREHOLDER MEETING**

### **First resolution**

Approval of the annual statutory accounts and management report for financial year ending December 31, 2020.

### **Second resolution**

Transfer of the year end loss of € 12,088,216 as of December 31, 2020, to the accumulated deficit account – No distribution of dividends.

### **Third resolution**

Approval of annual consolidated accounts and management report for financial year ending December 31, 2020.

### **Fourth resolution**

Acknowledgement of the special report of the Statutory Auditors on agreements with related parties – no related party agreement.

### **Fifth resolution**

Authorization for the Board to purchase its own shares within the limit of 10% of the share capital for either of the following purposes:

- to allocate Nicox shares as a means of payment or exchange, particularly in the event of external growth opportunities;
- to provide shares to employees or corporate officers of the Company or the Group, in particular under a profit sharing plan, a stock option plan or free share plan;
- to deliver shares upon exercise of rights attached to securities giving access to Nicox' share capital;
- to reduce the share capital by cancelling all or part of the shares purchased by the Company;
- to share trading and liquidity through a financial service provider pursuant to a contract complying with market practice approved by the French financial markets authority (*"Autorité des Marchés Financiers"*);
- for use in the context of all operations aiming to cover the undertakings of the Company with respect to financial instruments concerning, inter alia, the evolution of the trading price of the Company's stock;
- to implement any future market practice authorized by law or by the AMF.

This resolution, which replaces the resolution voted by the 2020 shareholder meeting, is granted until the annual shareholder meeting called to approve the accounts of the fiscal year ending December 31, 2021, subject to a maximum global amount of €10 million. This authorization can be used in the event of take-over bid or public exchange offer on the Company's securities.

### **Sixth resolution**

Approval of the information on the remuneration of the directors and corporate officers included in the corporate governance report pursuant to Article L. 22-10-9 of the French Commercial Code, as described in section 13.2 of the annual report for 2020.

### **Seventh resolution**

Approval of the components of the remuneration paid or granted to Michele Garufi, Chairman and CEO, in respect of fiscal year 2020, as described in section 13.2.1 of the annual report for 2020.

### **Eighth resolution**

Approval of the policy of remuneration of the directors and corporate officers as presented in section 13.1 of the annual report / universal registration document 2020 filed with the French financial markets authority.

### **Ninth resolution**

Decision to fix the maximum amount of the remuneration to be allocated among Board members to € 450,000 for the current financial year and the following financial years, until the shareholder meeting rules again on this matter.

### **Tenth resolution**

Renewal of the term of office as Board member of Michele Garufi for a period of 4 years ending upon the shareholder meeting called to approve the accounts as of December 31, 2024.

### **Eleventh resolution**

Renewal of the term of office as Board member of Luzi von Bidder for a period of 4 years ending upon the shareholder meeting called to approve the accounts as of December 31, 2024.

### **Twelfth resolution**

Renewal of the term of office as Board member of Ms. Adrienne Graves for a period of 4 years ending upon the shareholder meeting called to approve the accounts as of December 31, 2024.

### **Thirteenth resolution**

Renewal of the term of office as Board member of Ms. Lauren Silvernail for a period of 4 years ending upon the shareholder meeting called to approve the accounts as of December 31, 2024.

### **Fourteenth resolution**

Power for legal formality requirements.

## **SUMMARY OF THE RESOLUTIONS EXTRAORDINARY SHAREHOLDER MEETING**

### **First resolution**

Delegation of competence to the Board of Directors to proceed with increases in share capital (issuance of shares, equity securities giving right to other equity securities or debt securities and securities giving right to newly issued equity securities – in euro or other currencies) up to a maximum nominal amount of € 16,500,000 for a period of 26 months. Under this resolution, shareholders keep their preferential rights of subscription to the newly issued securities. This resolution includes the possibility of issuing debt securities giving right to shares up to a maximum amount € 100,000,000.

### **Second resolution**

Delegation of competence to the Board of Directors to proceed with increases in share capital (issuance of shares, equity securities giving right to other equity securities or debt securities and securities giving right to newly issued equity securities – in euro or other currencies) by way of public offering (except public offerings within the meaning of Article L. 411-2 1° of the French Commercial Code), subject to the maximum nominal amount of € 12,000,000 (and to the global nominal amount of € 16,500,000 provided for in resolution 1) for a period of 26 months. Under this resolution, shareholders waive their preferential rights of subscription to the newly issued securities. Accordingly, the price per equity security to be issued hereunder shall be equal to no less than a 10% discount on the last three trading days weighted average price (VWAP) of the Nicox share prior to the beginning of the public offering. This resolution also includes the possibility of issuing debt securities giving right to shares up to a maximum amount € 100,000,000, subject to the global nominal amount of € 100,000,000 provided for in resolution 1. This resolution can also be used to issue securities in connection with a public exchange offer initiated by the Company on the securities of another company pursuant to Article L. 22-10-54 of the French Commercial Code.

*(The maximum nominal amount of € 12,000,000 under this resolution applies globally to all the authorizations under resolutions 2, 3, 4, 7 and 8)*

### **Third resolution**

Delegation of competence to the Board of Directors to proceed with increases in share capital (issuance of shares, equity securities giving right to other equity securities or debt securities and securities giving right to newly issued equity securities – in euros or other currencies) by way of a private placement (qualified as a public offering within the meaning of Article L. 411-2 1° of the French Commercial Code, since the entry into force of the new EU prospectus regulation in July 2019), subject to the maximum nominal amount of € 12,000,000 and a maximum of 20% of the share capital per year (as well as to both (i) the nominal amount of € 12,000,000 provided for in resolution 2 and (ii) the global nominal amount of € 16,500,000 provided for in resolution 1) for a period of 26 months. Under this resolution, shareholders waive their preferential rights of subscription to the newly issued securities. Accordingly, the price per equity security to be issued hereunder shall be equal to no less than a 10% discount on the last three trading days weighted average price (VWAP) of the Nicox share prior to the beginning of the public offering. This resolution also includes the possibility of issuing debt securities giving right to shares up to a maximum amount € 100,000,000, subject to the global nominal amount of € 100,000,000 provided for in resolution 1.

*(The maximum nominal amount of € 12,000,000 applies globally to all the authorizations under resolutions 2, 3, 4, 7 and 8)*

#### Fourth resolution

Authorization to the Board of Directors, for a period of 26 months, to set the issue price of securities to be issued in the context of an increase of the share capital under resolutions 2 and 3 with pricing conditions deviating from the conditions set forth in such resolutions and within the limit of 10% of the share capital. Under this resolution, the price per equity security to be issued shall be equal to no less than a 15% discount on the last three trading days weighted average price (VWAP) of Nicox share prior to pricing.

#### Fifth resolution

**(overallotment)** Authorization to the Board of Directors, for a period of 26 months, to increase the number of securities to be issued in the context of an increase of the share capital (with or without shareholders preferential rights of subscription) under resolutions 1, 2, 3 and 7, subject to the maximum nominal amounts of:

- € 16,500,000 with respect to share capital increases under resolution 1
  - € 12,000,000 with respect to share capital increases under resolutions 2, 3 and 7,
- within 30 days of the end of the subscription period of the initial increase and within the limit of 15% of the amount thereof and under identical pricing conditions.

#### Sixth resolution

Delegation of competence to the Board of Directors, for a period of 26 months, to increase the share capital by incorporation of reserves, profits, premiums or other distributable amounts subject to the amount available for incorporation.

#### Seventh resolution

Delegation of powers to the Board of Directors, for a period of 26 months, to increase the share capital (issuance of shares, equity securities giving right to other equity securities or debt securities and securities giving right to newly issued equity securities), within the limit of 10% of said share capital and subject to both (i) the nominal amount of € 12,000,000 provided for in resolution 2 and (ii) the global nominal amount of € 16,500,000 provided for in resolution 1) for a period of 26 months, to remunerate capital contributions in kind consisting in securities of another entity. This resolution can be used in transactions where there is no public exchange offer within the meaning of Article L. 22-10-54 of the French Commercial Code.

*(The maximum nominal amount of € 12,000,000 applies globally to all the authorizations under resolutions 2, 3, 4, 7 and 8)*

#### Eighth resolution

**(PIPE)** Delegation of competence to the Board of Directors, subject to the maximum nominal amount of € 12,000,000 and for a period of 18 months, to increase the share capital (issuance of shares, equity securities giving right to other equity securities or debt securities and securities giving right to newly issued equity securities), for the benefit of (i) one or several companies or investment funds investing in the pharmaceutical/biotech sector, either French or foreign, or (ii) one or several credit institutions or authorized investment services providers committing to purchase such securities with a view to resell them to legal entities falling with the category defined in (i) above.

- reference price: last three trading days weighted average price (VWAP) prior to pricing;
- maximum authorized discount: 15%.

This resolution is subject to the maximum nominal amount of € 16,500,000 provided for in resolution 1 and to the maximum nominal amount of € 12,000,000 provided for in resolution 2.



Under this resolution, shareholders waive their preferential rights of subscription to the newly issued securities. This resolution also includes the possibility of issuing debt securities giving right to shares up to a maximum amount € 50,000,000, subject to the global nominal amount of € 100,000,000 provided for in resolution 1.

*(The maximum nominal amount of € 12,000,000 applies globally to all the authorizations under resolutions 2, 3, 4, 7 and 8)*

#### **Ninth resolution**

Delegation of competence to the Board of Directors, for a period of 26 months, to proceed with increases in share capital up to a maximum nominal amount of € 60,000 in connection with profit sharing plans reserved for the Company's employees and waiver of the shareholders' preferential subscription rights.

This resolution is subject to the maximum nominal amount of € 16,500,000 provided for in resolution 1.

#### **Tenth resolution**

Authorization granted to the Board of Directors, for a period of 38 months, to grant to employees and corporate officers of the Group free shares within the limit of 1,000,000 new or existing shares, it being specified that nominal increases in share capital under this resolution may not exceed € 1,000,000. The obtaining of the shares will be subject to the achievement of performance criteria to be fixed by the Board.

The Board may choose between two possibilities:

- the attribution of shares to the beneficiaries would only become firm at the expiry of a minimum one year period and, subsequently, the shares may not be sold before an additional minimum one year period;
- the attribution of shares to the beneficiaries would only become firm at the expiry of a minimum two year period in which case the shares may then be sold immediately.

These time limits may be extended by the Board of Directors.

This resolution replaces the resolution voted by the June 30, 2020 shareholder meeting.

#### **Eleventh resolution**

Authorization granted to the Board of Directors for a period of 38 months to grant to employees and corporate officers of the group, stock options giving right to subscribe up to 2,500,000 new or existing shares, it being specified that nominal increase in share capital under this resolution may not exceed € 2,500,000. The subscription price of the shares may not be less than 80% of the weighted average price of the Nicox share over the 20 trading days preceding the date of the decision of the board to grant the stock-options. The exercise of stock-options granted to Executive Committee members and to the CEO will be subject to the achievement of performance criteria to be fixed by the Board.

This resolution replaces the resolution voted by the June 30, 2020 shareholder meeting.

#### **Twelfth resolution**

Authorization to the Board of Directors to reduce the share capital by cancelling shares that have been repurchased up to a limit of 10% of the share capital over a 24-month period. This authorization is granted for a five year period.

### **Thirteenth resolution**

Power for legal formality requirements.

\* \* \*

## **NICOX SA**

Société anonyme au capital social de € 37 103 985

Siège social : Drakkar D - 2405 route des Dolines

06560 Valbonne, Sophia Antipolis

403 942 642 R.C.S. Grasse

N° d'immatriculation Insee : 403 942 642 00055

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### **RAPPORT DU CONSEIL D'ADMINISTRATION SUR LES RESOLUTIONS PROPOSEES**

#### **A L'ASSEMBLEE GENERALE ORDINAIRE ET A L'ASSEMBLEE GENERALE EXTRAORDINAIRE**

#### **CONVOQUEES LE 14 AVRIL 2021 SUR PREMIERE CONVOCATION**

(ET LE 28 AVRIL 2021 SUR SECONDE CONVOCATION)

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Chers Actionnaires,

Nous vous présentons ci-après les résolutions soumises à votre approbation dans le cadre de l'Assemblée générale ordinaire suivie d'une Assemblée générale extraordinaire appelées à se réunir le 14 avril 2021, sur première convocation.

Nous vous prions de vous reporter au chapitre 5 du rapport annuel (« Document d'enregistrement universel (URD), rapport financier annuel, rapport de gestion 2020 ») pour la présentation de l'activité de la Société et du groupe au cours de l'exercice écoulé.

L'ordre du jour de ces assemblées est le suivant :

#### ***Ordre du jour de l'Assemblée générale ordinaire***

- Approbation des comptes annuels de l'exercice clos le 31 décembre 2020 (résolution n° 1).
- Affectation du résultat de l'exercice clos le 31 décembre 2020 (résolution n° 2).
- Approbation des comptes consolidés de l'exercice clos le 31 décembre 2020 (résolution n° 3).
- Rapport spécial des Commissaires aux comptes sur les conventions réglementées (résolution n° 4).
- Autorisation donnée au Conseil d'administration d'acquérir des actions de la Société (résolution n° 5).
- Approbation des informations relatives à la rémunération des mandataires sociaux figurant dans le rapport sur le gouvernement d'entreprise en application de l'article L. 22-10-9 du Code de commerce (résolution n° 6).

- Approbation des éléments de la rémunération versée au cours de l'exercice clos le 31 décembre 2020 ou attribuée au titre du même exercice à Michele Garufi, Président-Directeur général (résolution n° 7).
- Approbation de la politique de rémunération applicable aux mandataires sociaux (résolution n° 8).
- Fixation du montant annuel de la rémunération des administrateurs (résolution n°9).
- Renouvellement du mandat d'un administrateur (Monsieur Michele Garufi) (résolution n°10).
- Renouvellement du mandat d'un administrateur (Monsieur Luzi von Bidder) (résolution n°11).
- Renouvellement du mandat d'un administrateur (Madame Adrienne Graves) (résolution n°12).
- Renouvellement du mandat d'un administrateur (Madame Lauren Silvernail) (résolution n°13).
- Pouvoirs à donner en vue des formalités (résolution n°14)

### ***Ordre du jour de l'Assemblée générale extraordinaire***

- Délégation de compétence consentie au Conseil d'administration pour émettre des actions, des titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que des valeurs mobilières donnant accès à des titres de capital à émettre de la Société, avec maintien du droit préférentiel de souscription des actionnaires (résolution n° 1).
- Délégation de compétence consentie au Conseil d'administration pour émettre des actions, des titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que des valeurs mobilières donnant accès à des titres de capital à émettre, avec suppression du droit préférentiel de souscription des actionnaires et par offre au public autre que celles visées à l'article L. 411-2 1° du Code monétaire et financier (résolution n° 2).
- Délégation de compétence consentie au Conseil d'administration pour émettre des actions, des titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que des valeurs mobilières donnant accès à des titres de capital à émettre, avec suppression du droit préférentiel de souscription des actionnaires et dans le cadre d'une offre au public visée à l'article L. 411-2 1° du Code monétaire et financier (résolution n° 3).
- Autorisation consentie au Conseil d'administration pour fixer le prix d'émission des titres à émettre dans le cadre des émissions réalisées en application des deuxième et troisième résolutions dans la limite de 10% du capital social par an (résolution n° 4).
- Autorisation consentie au Conseil d'administration pour augmenter le nombre de titres à émettre dans le cadre des émissions, avec ou sans droit préférentiel de souscription, réalisées en application des première, deuxième, troisième, quatrième et huitième résolutions (résolution n° 5).
- Délégation de compétence consentie au Conseil d'administration pour augmenter le capital par incorporation de réserves, bénéfices, primes ou autres sommes dont la capitalisation serait admise (résolution n° 6).
- Délégation de pouvoirs consentie au Conseil d'administration pour augmenter le capital dans la limite de 10 % du capital social en vue de rémunérer des apports en nature consentis à la Société en dehors d'une offre publique d'échange (résolution n° 7).
- Délégation de compétence consentie au Conseil d'administration pour augmenter le capital au bénéfice d'une catégorie de bénéficiaires, avec suppression du droit préférentiel de souscription des actionnaires à leur profit (résolution n° 8).

- Délégation de compétence consentie au Conseil d'administration pour augmenter le capital au profit des adhérents à un plan d'épargne d'entreprise avec suppression du droit préférentiel de souscription des actionnaires à leur profit (résolution n° 9).
- Autorisation donnée au Conseil d'administration pour procéder à des attributions gratuites d'actions existantes ou à émettre, emportant de plein droit renonciation des actionnaires à leur droit préférentiel de souscription (résolution n° 10).
- Autorisation donnée au Conseil d'administration pour consentir des options donnant droit à la souscription d'actions nouvelles de la Société ou à l'achat d'actions existantes, emportant de plein droit renonciation des actionnaires à leur droit préférentiel de souscription (résolution n° 11).
- Autorisation à conférer au Conseil d'administration à l'effet de réduire le capital social par annulation d'actions précédemment rachetées dans le cadre d'un programme de rachat d'actions (résolution n° 12).
- Pouvoirs à donner en vue des formalités (résolution n° 13).

## **I/ ASSEMBLEE GENERALE ORDINAIRE**

### **1. Approbation des comptes annuels de l'exercice clos le 31 décembre 2020 (résolution n° 1)**

Nous vous proposons d'approuver les comptes annuels de la Société de l'exercice clos le 31 décembre 2020 tels qu'ils sont présentés, ainsi que les opérations traduites par ces comptes ou résumées dans le « Document d'enregistrement universel (URD), rapport financier annuel, rapport de gestion » pour 2020 du Conseil d'administration et dans le rapport des Commissaires aux comptes sur les comptes annuels.

Nous vous précisons que ces comptes ne font état ni de charges non déductibles des bénéfices assujettis à l'impôt sur les sociétés visées par l'article 39-4 du Code général des impôts, ni de frais généraux visés par l'article 39-5 du Code général des impôts.

Les comptes sociaux, le rapport de gestion et le rapport des Commissaires aux comptes sont mis à votre disposition.

### **2. Affectation des résultats de l'exercice clos le 31 décembre 2020 (résolution n° 2)**

Nous vous proposons d'affecter la perte de l'exercice clos le 31 décembre 2020 s'élevant à la somme de (€12.088.216) au poste « Report à Nouveau » qui, après cette affectation, s'élèvera à (€455.731.717) débiteurs.

Nous vous rappelons, conformément aux dispositions légales, que la Société n'a procédé à aucune distribution de dividendes au titre des trois exercices précédents.

### **3. Approbation des comptes consolidés de l'exercice clos le 31 décembre 2020 (résolution n° 3)**

Nous vous proposons d'approuver les comptes consolidés de la Société de l'exercice clos le 31 décembre 2020 tels qu'ils sont présentés, ainsi que les opérations traduites par ces comptes ou résumées dans le rapport annuel du Conseil d'administration sur la gestion du Groupe tel qu'inclus dans le « Document d'enregistrement universel (URD), rapport financier annuel, rapport de gestion » pour 2020 et le rapport des Commissaires aux comptes sur les comptes consolidés.



Les comptes consolidés, le rapport annuel et le rapport des Commissaires aux comptes sont mis à votre disposition.

#### **4. Conventions visées aux articles L. 225-38 et suivants du Code de commerce (résolution n° 4)**

Aucun accord relevant des articles L. 225-38 et suivants du Code de commerce n'a été conclu au cours de l'exercice clos le 31 décembre 2020.

Nous vous invitons en conséquence à prendre acte des conclusions du rapport spécial des Commissaires aux comptes qui ne fait état d'aucune convention règlementée.

#### **5. Autorisation de procéder au rachat d'actions de la Société (résolution n° 5)**

Lors de l'Assemblée générale du 16 juin 2020, vous avez autorisé le Conseil d'administration à racheter un maximum de 10% du capital de la Société. Cette autorisation, qui avait été donnée pour une durée expirant à l'issue de l'Assemblée générale appelée à statuer sur les comptes de l'exercice clos le 31 décembre 2020 sans pouvoir excéder une durée de 18 mois. La Société n'a pas mis en œuvre de programme de rachat d'actions dans le cadre de cette autorisation.

Nous vous proposons de voter une nouvelle autorisation, qui remplacerait l'autorisation votée par l'Assemblée générale du 16 juin 2020, afin de permettre au Conseil d'administration d'acheter, selon les conditions prévues aux articles par les articles L. 22-10-62 et suivants du Code de commerce, les articles 241-1 et suivants du Règlement Général de l'Autorité des marchés financiers et le Règlement (UE) n° 596/2014 du 16 avril 2014 sur les abus de marché ("Règlement MAR") et le Règlement Délégué (UE) n° 2016/1052 du 8 mars 2016 complétant le Règlement MAR., un nombre d'actions de la Société représentant jusqu'à 10% du capital de la Société.

Ces acquisitions auraient pour objectifs :

- leur conservation et remise ultérieure à titre de paiement ou d'échange, notamment dans le cadre d'opérations de croissance externe ;
- la mise en œuvre de plans d'options d'achat d'actions, de plans d'attribution gratuite d'actions, d'opérations d'actionnariat salarié réservées aux adhérents à un plan d'épargne d'entreprise, conformément aux articles L. 3331-1 et suivants du Code du travail, ou d'allocation d'actions au profit des salariés et/ou dirigeants mandataires sociaux de la Société et des sociétés qui lui sont liées ;
- leur remise lors de l'exercice de droits attachés à des valeurs mobilières donnant accès au capital de la Société ;
- leur annulation, en tout ou partie, dans le cadre d'une réduction de capital ;
- l'animation du marché secondaire ou la liquidité des actions de la Société par un prestataire de services d'investissement dans le cadre d'un contrat de liquidité conforme à une pratique de marché admise par l'Autorité des marchés financiers ;
- leur utilisation dans le cadre de toute opération de couverture des engagements de la Société au titre d'instruments financiers portant notamment sur l'évolution du cours des actions de la Société ; ou
- la mise en œuvre de toute pratique de marché qui viendrait à être admise par la loi ou l'Autorité des marchés financiers.

Conformément à l'article L.22-10-62 du Code de commerce, le nombre d'actions acquises par la Société en vue de leur conservation et de leur remise ultérieure à titre de paiement ou en échange dans le cadre d'une opération de croissance externe ne pourrait excéder 5 % de son capital.

Ces opérations d'acquisition, de cession, de transfert ou d'échange d'actions pourraient être réalisées par tous moyens, notamment sur le marché (réglementé ou non), sur un système multilatéral de négociation (MTF), via un internalisateur systématique ou de gré à gré et, le cas échéant, notamment par voie d'acquisition ou de cession de blocs ou par recours à des instruments financiers dérivés (options, bons négociables...), à tout moment en ce compris en période d'offre publique portant sur les titres de la Société dans le respect de la réglementation en vigueur. La part du programme de rachat pouvant être effectuée par négociations de blocs pourrait atteindre la totalité du programme.

L'acquisition, la cession, le transfert ou l'échange de ces actions pourront intervenir à tout moment dans le respect des dispositions légales et réglementaires.

Le montant maximal de fonds destinés à la réalisation de ce programme d'achat d'actions serait de € 10 millions.

La présente autorisation serait donnée pour une durée de 18 mois à compter de la présente Assemblée générale.

Conformément aux dispositions de l'article L. 225-210 du Code de commerce, nous vous rappelons que les actions auto-détenues sont dépourvues de droit de vote et de droit aux dividendes. Nous vous rappelons également que conformément aux dispositions du même article, l'acquisition d'actions de la Société ne peut avoir pour effet d'abaisser les capitaux propres à un montant inférieur à celui du capital social augmenté des réserves non distribuables.

#### **6 - Approbation des informations relatives à la rémunération des mandataires sociaux figurant dans le rapport sur le gouvernement d'entreprise en application de l'article L. 22-10-9 du Code de commerce (résolution n°6)**

Le rapport sur le gouvernement d'entreprise expose l'ensemble des informations désormais requises sur les rémunérations des mandataires sociaux visées au I de l'article L. 22-10-9 du Code de commerce. Ces informations sont présentées à la section 13.2 du Document d'enregistrement universel, rapport financier annuel, rapport de gestion 2020 déposé auprès de l'Autorité des marchés financiers. Nous vous renvoyons en conséquence à cette section et vous demandons d'approuver, en application de l'article L. 22-10-34 du Code de commerce, les informations sur les rémunérations des mandataires sociaux qui y sont mentionnées.

#### **7. Approbation des éléments de la rémunération versée au cours de l'exercice clos le 31 décembre 2020 ou attribuée au titre du même exercice à Michele Garufi, Président-Directeur général (résolution n° 7)**

Le rapport sur le gouvernement d'entreprise décrit également les éléments composant la rémunération versée au cours de l'exercice clos le 31 décembre 2020 ou attribuée au titre du même exercice à Michele Garufi, Président-Directeur général. Ces informations sont présentées à la section 13.2.1 du Document d'enregistrement universel, rapport financier annuel, rapport de gestion 2020 déposé auprès de l'Autorité des marchés financiers. Nous vous renvoyons en conséquence à cette section et vous demandons d'approuver, en application de l'article L. 22-10-34 du Code de commerce, les éléments de rémunération versée ou attribuée à Michele Garufi qui y sont présentés.

#### **8. Approbation de la politique de rémunération applicable aux mandataires sociaux (résolution n° 8)**

Le rapport sur le gouvernement d'entreprise décrit enfin la politique de rémunération applicable aux mandataires sociaux (administrateurs et Président-Directeur Général) pour l'exercice 2021 telle qu'arrêtée par le Conseil d'administration. Cette politique est présentée à la section 13.1 du Document d'enregistrement universel, rapport financier annuel, rapport de gestion 2020 déposé auprès de l'Autorité des marchés financiers. Nous vous renvoyons en conséquence à cette section et vous demandons d'approuver, en application de l'article L. 22-10-8 du Code de commerce, la politique de rémunération des mandataires sociaux qui y est présentée.

#### **9. Fixation du montant annuel de la rémunération des administrateurs (résolution n° 9)**

Le montant de la rémunération à répartir entre les administrateurs (anciennement dénommés "jetons de présence") était fixé jusqu'ici à € 350 000 par exercice. Nous vous prions d'augmenter ce montant et de fixer le montant maximum de la rémunération à répartir entre les administrateurs à € 450 000 euros pour l'exercice en cours et les exercices suivants, et ce jusqu'à nouvelle décision de l'Assemblée générale. Cette proposition d'augmentation du montant global alloué a été jugée opportune compte tenu du nombre de séances du Conseil et de l'implication des administrateurs. Les modalités de répartition de cette rémunération sont définies dans la politique de rémunération pour l'exercice 2021 qui vous est soumise par ailleurs lors de cette assemblée.

#### **10. Renouvellement du mandat d'un administrateur (Monsieur Michele Garufi) (résolution n° 10)**

Nous vous proposons de renouveler le mandat d'administrateur de Monsieur Michele Garufi pour une durée de quatre années qui prendra fin à l'issue de l'Assemblée générale qui statuera sur les comptes de l'exercice clos le 31 décembre 2024.

Michele Garufi est Président Directeur Général de la Société et l'un de ses fondateurs, en 1996. Avant de fonder la Société Nicox, Michele Garufi était Vice-Président de la Division Internationale et Directeur des Activités Licences du Groupe Recordati ainsi que Directeur Général de la filiale espagnole de Recordati Italie. Auparavant, il a été Directeur de la Division Internationale d'Italfarmaco (1988-1992), Assistant du Directeur Général de Poli Chimica (1984-1988), Assistant du Président de Medea Research (1983) et Directeur Technique de l'une des filiales italiennes du groupe français Lipha (1978-1982). Michele Garufi est actuellement co-fondateur et membre du Conseils d'administration de LaMed, une société privée italienne fournissant des services à l'industrie pharmaceutique ainsi que co-fondateur et membre du Conseil d'administration de NanoRetinal Inc, une société de R&D axée sur les maladies oculaires rares. Précédemment, il a été membre des Conseils d'administration de Novuspharma SpA, Suisse, Novexel SA, France, Lica SA., Suède, Scharper SpA, Italie, Delife Srl, Italie, Relivia Srl, Italie, OncoBioTek Srl, Italie, et VISUfarma (Iris TopCo), Royaume-Uni. Michele Garufi a été diplômé avec mention en chimie pharmaceutique de l'Université de Milan en 1977 et a également obtenu un diplôme de pharmacien en 1989. Mr Garufi a été membre de l'équipe nationale italienne de natation.

#### **11. Renouvellement du mandat d'un administrateur (Monsieur Luzi von Bidder) (résolution n° 11)**

Nous vous proposons de renouveler le mandat d'administrateur de Monsieur Luzi von Bidder pour une durée de quatre années qui prendra fin à l'issue de l'Assemblée générale qui statuera sur les comptes de l'exercice clos le 31 décembre 2024.

Luzi A. von Bidder a été coopté administrateur de Nicox en août 2014. En tant qu'administrateur mais aussi de membre du Comité d'audit et du Comité de gouvernance d'entreprise, il apporte une expertise précieuse au gouvernement et à la définition de la stratégie de la Société. Son mandat viendra à expiration à l'issue de l'Assemblée générale appelée à statuer sur les comptes de l'exercice clos le 31 décembre 2020. Il était président d'Acino Holding AG jusqu'en 2013. Auparavant, Luzi von Bidder a

occupé la fonction de Président directeur général de Novartis Ophthalmics AG. Il a également été membre du comité exécutif de Novartis Pharma et a occupé différents postes chez Ciba-Geigy. Luzi von Bidder est actuellement membre du Conseil d'administration de Ferring Pharmaceuticals, Ixodes AG, Oculocare, Orasis, et d'EyeSense GmbH dont il est également Président du conseil. M. von Bidder est titulaire d'une licence en sciences économiques de l'université HSG (St. Gallen, Suisse). Il est âgé de 65 ans. Il peut être contacté Kirchenweg 5, 8008, Zürich, Suisse. Il détient 10 000 actions Nicox.

**12. Renouvellement du mandat d'un administrateur (Madame Adrienne Graves) (résolution n° 12)**

Nous vous proposons de renouveler le mandat d'administrateur de Madame Adrienne Graves pour une durée de quatre années qui prendra fin à l'issue de l'Assemblée générale qui statuera sur les comptes de l'exercice clos le 31 décembre 2024.

Madame Adrienne Graves a été cooptée administrateur de Nicox en août 2014. En tant qu'administrateur mais aussi de Président du Comité des rémunérations et membre du Comité Science et Technologie, elle apporte une expertise précieuse au gouvernement et à la définition de la stratégie de la Société. Son mandat viendra à expiration à l'issue de l'Assemblée générale appelée à statuer sur les comptes de l'exercice clos le 31 décembre 2020. Scientifique dans le domaine oculaire de formation, Mme Graves est un leader international de l'ophtalmologie dans l'industrie pharmaceutique. Elle a occupé le poste de Président directeur général de Santen Inc. de 1995 à 2010, où elle a établi une forte présence à l'international, conduit l'approbation et la commercialisation de plusieurs produits ophtalmiques et a dirigé des équipes internationales au travers d'acquisitions et de partenariats. Avant les quinze années passées au sein de Santen, le Dr Graves a occupé pendant 9 ans diverses fonctions chez Alcon Laboratories Inc d'abord en tant que Senior Scientist pour la mise en place du premier laboratoire de fonction visuelle d'Alcon, puis elle a occupé des postes de direction en R&D, notamment le développement clinique dans de multiples domaines thérapeutiques en tant que Director of International Ophthalmology. Le Dr Graves est administrateur indépendant d'Oxurion NV, une société belge, Greenbrook TMS, une société canadienne, Iveric Bio, une société américaine, Qlaris Bio, TherOptix et Surface Ophthalmics, des sociétés privées américaines. Le Docteur Graves est également administrateur de l'*American Society of Cataract Refractive Surgery Foundation (ASCRS)* aux Etats-Unis, de la *Glaucoma Research Foundation* aux Etats-Unis, de *Retina Global, Himalayan Cataract Project*, fondation américaine et de la *Foundation Fighting Blindness* aux Etats-Unis. Mme Graves occupe le poste d'administrateur émérite de l'*American Academy of Ophthalmology Foundation*. Elle a été précédemment membre des conseils d'administration d'Encore Vision de 2011 à 2017, société acquise par Novartis, d'Envisia Therapeutics de 2014 à 2017, société acquise par Aerie Pharmaceuticals, de TearLab Corporation de 2005 à 2018, d'Akorn de 2012 à 2020 et d'Aerpio Therapeutics de 2012 à 2017. Elle a co-fondé OWL (Ophthalmic World Leaders) et Glaucoma 360. Le Dr Graves a obtenu une licence en psychologie avec mention de l'Université Brown (Etats-Unis), un doctorat en psychobiologie de l'Université du Michigan (Etats-Unis) complété par un stage postdoctoral en neurosciences visuelles à l'Université de Paris. Elle est âgée de 66 ans. Mme Graves peut être contactée au 110 N. Corcoran Street #2401 (NC) 27701 Durham, Etats Unis. Elle ne détient aucune action Nicox.

**13. Renouvellement du mandat d'un administrateur (Madame Lauren Silvernail) (résolution n° 13)**

Nous vous proposons de renouveler le mandat d'administrateur de Madame Lauren Silvernail pour une durée de quatre années qui prendra fin à l'issue de l'Assemblée générale qui statuera sur les comptes de l'exercice clos le 31 décembre 2024.

Lauren Silvernail a été nommé administrateur de Nicox en mai 2017. En tant qu'administrateur mais aussi de Président du Comité de gouvernance d'entreprise et membre du Comité d'audit, elle apporte une expertise précieuse au gouvernement et à la définition de la stratégie de la Société. Son mandat viendra à expiration à l'issue de l'Assemblée générale appelée à statuer sur les comptes de l'exercice

clos le 31 décembre 2020. Madame Silvernail est actuellement *Chief Financial Officer* et *Executive Vice President of Corporate Development* d'Evolus Inc. Précédemment, elle était *Chief Financial Officer* et *Chief Business Officer* de Revance Therapeutics, Inc. Avant de rejoindre Revance Therapeutics, Inc., Madame Silvernail était *Chief Financial Officer* et *Vice President of Corporate Development* d'ISTA Pharmaceuticals, Inc. de 2003 à 2012. Auparavant, de 1995 à 2003, Madame Silvernail a occupé différents postes opérationnels et de développement d'entreprise et, en dernier lieu, la fonction de *Vice President of Business Development*, chez Allergan Inc. Auparavant, de 1990 à 1994, elle a été associé gérant de Glenwood Ventures et membre du conseil d'administration de plusieurs sociétés de Glenwood. Madame Silvernail a commencé sa carrière chez Varian et Bio-Rad Laboratories. Elle a obtenu un M.B.A. à l'Université de Californie, Los Angeles et une licence en biophysique à l'Université de Californie à Berkeley. Elle est âgée de 61 ans. Elle peut être contactée au 10 Hertford, CA 92657 Newport Coast, Etats-Unis. Elle ne détient aucune action de Nicox.

**14. Pouvoirs pour l'accomplissement des formalités (résolution n° 14)**

Nous vous proposons de donner tous pouvoirs au porteur d'une copie ou d'un extrait du procès-verbal des présentes en vue de l'accomplissement des formalités légales.



## **II/ ASSEMBLEE GENERALE EXTRAORDINAIRE**

- 1. Délégations générales de compétence au Conseil d'administration en vue de l'émission d'actions, de titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que de valeurs mobilières donnant accès à des titres de capital à émettre, avec ou sans droit préférentiel de souscription des actionnaires (résolutions n° 1, 2, 3 et 8) ou par incorporation de réserves (résolution n° 6), et autorisation d'ajuster certaines caractéristiques desdites émissions dans certaines conditions (résolutions n° 4 et 5).**

Nous vous proposons de consentir des délégations de compétence au Conseil d'administration afin de lui permettre d'émettre des actions, des titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que des valeurs mobilières donnant accès à des titres de capital à émettre, avec (résolution n° 1) ou sans droit préférentiel de souscription des actionnaires (résolutions n° 2, 3 et 8), pour une durée de 18 mois (résolution n° 8) à 26 mois (résolutions n° 1, 2 et 3), dans la limite d'un plafond nominal global d'augmentation de capital de € 16.500.000 et d'un sous plafond cumulatif de € 12.000.000 s'agissant des autorisations sans droit préférentiel de souscription prévues aux résolutions n° 2, 3 et 8.

Nous vous proposons également d'autoriser le Conseil d'administration à fixer le prix d'émission des titres à émettre dans le cadre des augmentations de capital sans droit préférentiel de souscription et par voie d'offre au public (résolutions n° 2 et 3) en dérogeant au prix minimum légal dans la limite de 10% du capital social par an pour permettre au Conseil une plus grande flexibilité pour tenir compte des conditions de marché (résolution n° 4).

Nous vous proposons enfin d'autoriser le Conseil d'administration à augmenter le nombre de titres à émettre dans la limite de 15 % de l'émission initiale dans tous les cas en cas de demande excédentaire (résolution n° 5).

Si vous approuvez ces résolutions, le Conseil aurait la possibilité :

- (1) de décider l'émission d'actions, de titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que de valeurs mobilières donnant accès à des titres de capital à émettre, avec maintien du droit préférentiel de souscription des actionnaires (résolution n° 1) :
  - le montant nominal global des augmentations de capital serait limité à € 16.500.000,
  - la somme revenant ou devant revenir à la Société pour chacune des actions émises serait au moins égale à la valeur nominale de l'action à la date d'émission desdites valeurs mobilières,
  - le montant nominal global des valeurs mobilières représentatives de titres de créance donnant accès au capital ou droit à l'attribution de titres de créance serait au maximum de € 100 millions ou la contre-valeur de ce montant en cas d'émission en monnaie étrangère ou en unités de comptes fixées par référence à plusieurs monnaies,

- les actionnaires bénéficieraient d'un droit préférentiel de souscription à titre irréductible et le Conseil d'administration aurait en outre la faculté de leur conférer un droit de souscrire à titre réductible ; étant précisé que la souscription pourrait être opérée soit en espèces, soit par compensation avec des créances certaines, liquides et exigibles,
  - si les souscriptions à titre irréductible et, le cas échéant, à titre réductible, n'absorbaient pas la totalité d'une émission d'actions ou de valeurs mobilières, le Conseil pourrait offrir au public tout ou partie des titres non souscrits, les répartir librement, totalement ou partiellement et/ou limiter le montant de l'augmentation de capital au montant des souscriptions à conditions qu'il atteigne au moins 75 % de l'augmentation de capital décidée.
- (2) de procéder à l'émission d'actions, de titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que de valeurs mobilières donnant accès à des titres de capital à émettre, avec suppression du droit préférentiel de souscription des actionnaires (résolutions n° 2, 3, 4 et 8) :
- le placement des titres serait effectué soit par voie d'une offre au public, exceptées les formes d'offres au public visées par l'article L. 411-2 1° du Code monétaire et financier (résolution n° 2), soit, comme le permet l'article L. 411-2 1° du Code monétaire et financier, par voie d'une offre au public auprès notamment d'investisseurs qualifiés et de gérants de portefeuille (résolution n° 3), soit à catégorie de personnes conformément à l'article L. 225-138 du Code de commerce (résolution n° 8), Nous vous précisons que depuis l'entrée en vigueur en juillet 2019 du règlement européen sur les prospectus (n° 2017/1129 du 14 juin 2017 (le "Règlement Prospectus"), toutes les offres sont désormais qualifiées d'offres au public, y compris ce qui était auparavant défini comme un placement privé. Néanmoins, il existe différents types d'offres au public, dont l'un reprend les contours de ce qui précédemment qualifié de placement privé, d'où la persistance de deux résolutions distinctes.
  - le droit préférentiel de souscription des actionnaires serait supprimé mais le Conseil pourrait leur conférer un droit de priorité sur tout ou partie de l'émission, à l'exception du cas d'une augmentation de capital réservée, pour une émission donnée, à l'une des catégories de personnes visées à la résolution n° 8, à savoir (i) toute société ou fonds gestionnaire d'épargne collective de droit français ou de droit étranger investissant dans le secteur pharmaceutique/biotechnologique ou (ii) tout établissement de crédit ou tout prestataire de services d'investissement habilité s'engageant à les acquérir pour les revendre aux personnes visées au (i) ci-dessus,
  - la somme revenant ou devant revenir à la Société pour chacune des actions émises (la souscription pouvant être opérée soit en espèces, soit par compensation avec des créances certaines, liquides et exigibles) serait au moins égale à la valeur minimum fixée par la loi et les règlements applicables au moment où il est fait usage de la délégation, soit actuellement à la moyenne pondérée des cours de l'action de la Société sur le marché réglementé d'Euronext à Paris lors des trois dernières séances de bourse précédant le début de l'offre au public au sens du Règlement Prospectus, éventuellement diminuée d'une décote maximale de 10 %, après correction s'il y a lieu, de ce montant pour tenir compte de la différence de date de jouissance (résolutions n° 2 et 3),
  - par dérogation aux conditions de fixation du prix susmentionnée, dans la limite de 10% du capital social par an, la somme revenant ou devant revenir à la Société pour chacune des actions

émises serait au moins égale à la moyenne pondérée des cours de l'action de la Société sur le marché réglementé d'Euronext à Paris lors des trois dernières séances de bourse précédant la fixation du prix d'émission, éventuellement diminuée d'une décote maximale de 15 %. Ces modalités distinctes permettraient au Conseil de faciliter une levée de fonds par offre au public en fonction des circonstances de marché et de l'appétit des investisseurs (résolution n° 4) ; elles sont identiques à celles proposées pour les émissions réservées à catégorie de personnes visées ci-après,

- s'agissant des émissions à catégorie de personnes (résolution n° 8), pour lesquelles le Conseil d'administration fixerait la liste précise des bénéficiaires au sein, pour une émission donnée, de l'une des catégories susmentionnées au profit de laquelle le droit préférentiel de souscription aurait été supprimé, la somme revenant ou devant revenir à la Société pour chacune des actions émises serait au moins égale à la moyenne pondérée des cours de l'action de la Société sur le marché réglementé d'Euronext à Paris lors des trois dernières séances de bourse précédant la fixation du prix d'émission, éventuellement diminuée d'une décote maximale de 15 % ; la possibilité d'une décote pouvant aller jusqu'à 15 % visant à faciliter l'opération en fonction des conditions de marché,
  - dans chaque cas (résolutions n° 2, 3, 4 et 8), le montant nominal des augmentations de capital social susceptibles d'être réalisées immédiatement ou à terme ne pourrait excéder un montant nominal global pour toutes les autorisations de € 12.000.000 (ni 20 % du capital par an, s'agissant d'une offre au public régie par l'article L. 411-2 1° du Code monétaire et financier – résolution n° 3), étant précisé que ce montant s'imputerait sur le plafond nominal global de € 16.500.000,
  - de la même façon, dans chaque cas (résolutions n° 2, 3, 4 et 8), le montant nominal global des valeurs mobilières représentatives de titres de créance donnant accès au capital ou à l'attribution de titres de créance, susceptibles d'être émises serait au maximum de € 100 millions (résolutions 2, 3 et 4) ou € 50 millions (résolution 8) ou la contre-valeur de ce montant en cas d'émission en monnaie étrangère ou en unités de compte fixées par référence à plusieurs monnaies, étant précisé que ce montant s'imputerait sur le plafond de € 100 millions prévue par la résolution n° 1,
  - le Conseil d'administration pourrait faire usage de la délégation consentie aux termes de la résolution n° 2 à l'effet de rémunérer des titres apportés à une offre publique d'échange initiée par la Société répondant aux conditions fixées par l'article L. 22-10-54 du Code de commerce,
  - dans le cadre d'une offre au public (résolutions n° 2 et 3), si les souscriptions n'absorbaient pas la totalité d'une émission d'actions ou de valeurs mobilières, le Conseil pourrait limiter l'émission au montant des souscriptions reçues.
- (3) d'augmenter le nombre de titres à émettre en cas d'augmentation de capital avec ou sans droit préférentiel de souscription (résolution n° 5, en application des résolutions n° 1, 2, 3, 4 et 8) :
- dans les trente jours de la clôture de la souscription dans la limite de 15 % de l'émission initiale et au même prix que celui retenu pour l'émission initiale,
  - le Conseil aurait ainsi la possibilité d'accroître le volume de l'augmentation de capital en cas de succès de l'opération,

- le montant nominal maximal des augmentations de capital susceptibles d'être réalisées s'imputerait sur le plafond nominal d'augmentation de capital fixé par chacune des résolutions au titre de laquelle l'émission initiale a été décidée, soit € 16.500.000 pour la première résolution et € 12.000.000 pour les deuxième, troisième, quatrième et huitième résolutions.

Si vous approuvez ces résolutions, le Conseil d'administration établirait à chaque usage de ces autorisations, conformément aux dispositions réglementaires applicables, un rapport destiné aux actionnaires décrivant les conditions définitives de l'opération et indiquant (1) l'effet dilutif potentiel de l'émission des valeurs mobilières sur la situation de chaque actionnaire, (2) l'incidence potentielle de l'émission des valeurs mobilières sur la quote-part des capitaux propres par action et (3) l'incidence théorique potentielle de l'émission des valeurs mobilières sur la valeur boursière de l'action de la Société.

Nous vous demandons également de consentir une autorisation au Conseil d'administration pour lui permettre de réaliser une augmentation du capital social de la Société par incorporation de réserves, primes, bénéfices ou autres sommes dont la capitalisation serait admise dans la limite des sommes pouvant être incorporées au capital. Le montant des augmentations de capital à ce titre serait indépendant du plafond global d'augmentation de capital de € 16,500,000 fixé par la première résolution. Cette délégation serait valable pour une durée de 26 mois (résolution n° 6).

Nous vous précisons que le Conseil d'administration ne pourrait faire usage d'aucune de ces délégations en période d'offre publique sur les titres de la Société.

## **2. Délégation de pouvoir au Conseil d'administration en vue d'augmenter le capital afin de rémunérer des apports en nature consentis à la Société (résolution n° 7)**

Nous vous invitons à déléguer au Conseil d'administration les pouvoirs nécessaires pour augmenter le capital social, en une ou plusieurs fois, dans la limite de 10 % du montant du capital social au jour d'utilisation de la délégation, par émission d'actions, de titres de capital donnant accès à d'autres titres de capital de la Société ou donnant droit à l'attribution de titres de créances ainsi que de valeurs mobilières donnant accès à des titres de capital à émettre, sur le rapport du ou des Commissaires aux apports, en vue de rémunérer des apports en nature consentis à la Société et constitués de titres de capital ou de valeurs mobilières donnant accès au capital, lorsque les dispositions de l'article L. 22-10-54 du Code de commerce ne sont pas applicables.

Cette délégation permettrait au Conseil d'administration de financer dans les meilleurs délais, par émission de titres, des acquisitions de titres d'une société, soit dont les actions ne sont pas cotées, soit dont les actions sont cotées (i) si elles ne le sont pas sur un marché réglementé de l'EEE ou de l'OCDE ou (ii) si l'opération n'est pas réalisée dans le cadre d'une offre publique d'échange.

La délégation ainsi conférée au Conseil serait valable pour une durée de 26 mois à compter de la présente Assemblée générale et ne pourrait être utilisée par le Conseil d'administration en période d'offre publique sur les titres de la Société.

## **3. Augmentation de capital au profit des adhérents à un plan d'épargne d'entreprise (résolution n° 9)**

Nous vous rappelons qu'aux termes des dispositions de l'article L. 225-129-6 du Code de commerce, il est obligatoire de soumettre à toute Assemblée générale appelée à se prononcer sur une augmentation de capital un projet de résolution tendant à réaliser une augmentation de capital dans les conditions prévues aux articles L. 3332-1 et suivants du Code du travail et de l'article L. 225-138-1 du Code de commerce, à savoir réservée aux adhérents d'un plan d'épargne entreprise.

En conséquence, nous vous proposons de déléguer votre compétence au Conseil d'administration afin d'augmenter le capital, par émission d'actions ou d'autres titres donnant accès au capital de la Société, avec suppression du droit préférentiel de souscription des actionnaires au profit des salariés de la Société ou des entreprises françaises ou étrangères qui lui sont liées au sens de l'article L. 225-180 du Code de commerce et de l'article L. 3344-1 du Code du travail qui adhèrent ou adhèreront à un plan d'épargne entreprise. Dans ce cadre :

- le montant nominal des augmentations de capital social susceptibles d'être réalisées immédiatement ou à terme ne pourrait excéder un montant nominal global de € 60.000, étant précisé que ce montant s'imputerait sur le plafond nominal global de € 16.500.000 prévu à la résolution n° 1,
- le prix de souscription des actions nouvelles serait égal à 70 % ou 60 % de la moyenne pondérée des cours de l'action de la Société sur le marché réglementé d'Euronext à Paris lors des 20 séances de bourse précédant le jour de la décision fixant la date d'ouverture des souscriptions, selon la durée d'indisponibilité prévue par le plan d'épargne entreprise, le Conseil pouvant toutefois réduire ou supprimer cette décote,
- le Conseil d'administration pourrait, en application de l'article L. 3332-21 du Code du travail, substituer tout ou partie de la décote par l'attribution gratuite d'actions ou d'autres titres donnant accès au capital de la Société, existants ou à émettre, l'avantage total résultant de cette attribution et, le cas échéant, de la décote mentionnée ci-dessus, ne pouvant excéder l'avantage total dont auraient bénéficié les adhérents au plan d'épargne si cet écart avait été de 20 % ou de 30 % selon la durée d'indisponibilité prévue par le plan,
- le Conseil d'administration pourrait également décider l'attribution, à titre gratuit, d'actions à émettre ou déjà émises ou d'autres titres donnant accès au capital de la Société à émettre ou déjà émis, au titre de l'abondement.

La délégation ainsi conférée au Conseil d'administration serait valable pour une durée de 26 mois à compter de la présente Assemblée générale.

Si vous approuvez cette résolution, le Conseil d'administration établirait, conformément aux dispositions réglementaires applicables, lors de chaque émission, un rapport complémentaire destiné aux actionnaires décrivant les conditions définitives de l'opération et indiquant (1) l'effet dilutif potentiel de l'émission des valeurs mobilières sur la situation de chaque actionnaire, (2) l'incidence potentielle de l'émission des valeurs mobilières sur la quote-part des capitaux propres par action et (3) l'incidence théorique potentielle de l'émission des valeurs mobilières sur la valeur boursière de l'action de la Société.

**4. Autorisation donnée au Conseil d'administration pour procéder à l'attribution gratuite d'actions existantes ou à émettre (résolution n° 10)**



Nous vous demandons d'autoriser le Conseil d'administration, conformément aux articles L. 225-197-1 et suivants, L. 22-10-59 et L. 22-10-60 du Code de commerce, à procéder, en une ou plusieurs fois, à des attributions gratuites d'actions existantes ou à émettre de la Société, au profit des membres du personnel ou de certaines catégories d'entre eux qu'il déterminerait parmi les salariés et les mandataires sociaux éligibles de la Société ou des sociétés liées au sens de l'article L. 225-197-2 du Code de commerce.

Cette attribution gratuite d'actions aurait pour objectif d'offrir au Conseil d'administration un dispositif attractif dans le cadre de la politique de recrutement de la Société, favorisant la fidélisation des salariés et des mandataires sociaux bénéficiaires et suscitant chez ceux-ci une motivation supplémentaire.

Le Conseil d'administration déterminerait l'identité des bénéficiaires des attributions ainsi que les conditions et les critères d'attribution des actions, étant précisé que l'acquisition définitive des actions serait soumise à des conditions de performance qui seront fixées par le Conseil d'administration au moment de leur attribution.

Les attributions gratuites d'actions effectuées en vertu de cette autorisation ne pourraient excéder 1.000.000 actions existantes ou nouvelles d'une valeur nominale d'un euro, le montant nominal maximum des augmentations de capital susceptibles d'être réalisées immédiatement ou à terme en vertu de la présente résolution ne pouvant excéder € 1.000.000. A cette fin, l'Assemblée générale autoriserait, en tant que de besoin, le Conseil d'administration à augmenter le capital social par incorporation de réserves à due concurrence. Le nombre total d'actions attribués gratuitement dans le cadre de la présente autorisation ne pourrait excéder 10 % du capital social de la Société à la date de la décision d'attribution, conformément à l'article L. 225-197-1 I du Code de commerce

L'autorisation serait consentie pour une durée de 38 mois à compter de la présente Assemblée générale. Elle mettrait fin pour la partie non utilisée à la précédente autorisation ayant le même objet consentie par l'Assemblée du 30 juin 2020.

Le Conseil informerait chaque année l'Assemblée générale, dans les conditions légales et réglementaires, des opérations réalisées dans le cadre de la présente autorisation.

## **5. Autorisation donnée au Conseil d'administration pour consentir des options donnant droit à la souscription d'actions nouvelles ou à l'achat d'actions existantes (résolution n° 11)**

Nous vous demandons d'autoriser le Conseil à consentir, en une ou plusieurs fois, aux salariés et mandataires sociaux détenant moins de 10 % du capital de la Société, ou à certaines catégories d'entre eux, de la Société et des sociétés qui lui seraient liées au sens de l'article L. 225-180 du Code de commerce, des options donnant droit à la souscription d'actions nouvelles de la Société ou à l'achat d'actions existantes, dans la limite de 2.500.000 actions existantes ou nouvelles, d'une valeur nominale de un euro chacune.

Cette attribution d'options de souscription ou d'achat d'actions aurait pour objectif d'attirer et de fidéliser les salariés et mandataires sociaux, de leur donner une motivation supplémentaire et en conséquence de promouvoir la réussite de la Société.

L'autorisation serait consentie pour une durée de 38 mois à compter de la présente Assemblée générale.

Le Conseil d'administration déterminerait l'identité des bénéficiaires des attributions ainsi que les conditions et les critères d'exercice des options, étant précisé que, s'agissant des bénéficiaires qui sont membres du Comité de direction ou mandataire social, l'exercice des options serait soumis à des conditions de performance qui seraient fixées par le Conseil d'administration au moment de leur attribution.

Le prix de souscription des actions nouvelles ou d'achat des actions existantes par exercice des options serait déterminé par le Conseil le jour de l'attribution des options de la façon suivante :

- Le prix de souscription des actions nouvelles ne pourra être inférieur à 80 % de la moyenne pondérée des cours de l'action de la Société sur le marché réglementé d'Euronext à Paris lors des 20 séances de bourse précédant la séance du Conseil.
- Le prix d'achat des actions existantes ne pourra être inférieur au plus élevé des deux montants suivants : (a) 80 % de la moyenne pondérée des cours de l'action de la Société sur le marché réglementé d'Euronext à Paris lors des 20 séances de bourse précédant la séance du Conseil et (b) le cours moyen d'achat des actions détenues par la Société au titre de l'article L. 22-10-62 du Code de commerce.
- Si les actions de la Société cessaient d'être admises aux négociations sur un marché réglementé, le prix de souscription ou d'achat des actions par exercice des options sera déterminé par le Conseil conformément à l'article L. 225-177 du Code de commerce. Dans la seule hypothèse des options d'achat d'actions, le prix ainsi déterminé par le Conseil ne pourra en aucun cas être inférieur au prix moyen d'achat des actions éventuellement détenues par la Société.

Les options devraient être exercées dans un délai maximum de huit ans à compter de leur attribution par le Conseil d'administration, celui-ci pouvant toutefois réduire ce délai pour les bénéficiaires résidents de pays dans lesquels une durée inférieure est prévue par la loi.

L'autorisation serait consentie pour une durée de 38 mois à compter de la présente Assemblée générale. Elle mettrait fin pour la partie non utilisée à la précédente autorisation ayant le même objet consentie par l'Assemblée du 30 juin 2020.

Le Conseil informerait chaque année l'Assemblée générale, dans les conditions légales et réglementaires, des opérations réalisées dans le cadre de la présente autorisation.

## **6. Annulation d'actions rachetées dans le cadre d'un programme de rachat d'actions (résolution n° 12)**

Nous vous proposons d'autoriser le Conseil d'administration, le cas échéant, à annuler tout ou partie des actions qu'il aura rachetées et à réduire corrélativement le capital social dans la limite de 10 % du capital de la Société par périodes de 24 mois. Cette autorisation sera valable pour une période de cinq années expirant lors de l'Assemblée générale appelée à approuver les comptes annuels au 31 décembre 2025. Cette résolution priverait d'effet pour sa partie non utilisée l'autorisation ayant le même objet consentie par l'Assemblée générale extraordinaire du 30 juin 2020.

## **7. Pouvoirs en vue des formalités (résolution n° 13)**

Nous vous proposons de donner tous pouvoirs au porteur d'une copie ou d'un extrait du procès-verbal des présentes en vue de l'accomplissement des formalités légales.

Au cours de l'Assemblée générale vous seront présentés, notamment, les rapports des Commissaires aux comptes qui vous donneront leur avis sur la proposition de suppression du droit préférentiel de souscription des actionnaires au titre des différentes délégations de compétence aux fins d'augmentation du capital social sur lesquelles nous vous demandons de vous prononcer aujourd'hui.

Nous vous remercions de faire confiance au Conseil d'administration pour toutes décisions à prendre concernant les modalités d'exécution des opérations que nous vous avons présentées.

C'est dans ces conditions que nous vous demandons d'approuver les résolutions qui vous sont soumises par le Conseil d'administration.

**Le Conseil d'administration**

## **Nicox's Ordinary and Extraordinary General Meetings convened for April 14, 2021**

### **Summary of the situation during the financial year 2020**

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- Extract of the 2020 Annual Report (*Document d'enregistrement universel, rapport annuel et rapport de gestion*) filed with the French Autorité des Marchés Financiers (AMF) on March 1, 2021— Chapters 3, 4 and 5
- Press releases on the 2020 annual results issued on March 1, 2021 and those issued after this date

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**3. RISK FACTORS AND INTERNAL CONTROL**

Under the provisions of article 16 of Regulation(UE) 2017/1129 of the European Parliament and the Council, this section presents the key risks which on the date of this universal registration document could have a material adverse effect on its business, financial status, operating results, or ability to achieve its objectives. However, the occurrence of risks unknown on the date of this universal registration document or not considered likely to have a material adverse effect on the date of this universal registration document cannot be excluded. Each year the Board of Directors reviews the risks to which the Company is exposed and issues an opinion as to their importance.

The key risks to which the Company considers it is exposed are presented according to the following categories, without any order of importance: (i) risks relating to the Company's financial position and capital requirements, (ii) risks relating to the products developed by the Company, regulatory authorizations and sale, (iii) risks relating to a dependence on third parties, (iv) risks relating the Company's intellectual property, (iv) risks relating to the Company's organization, structure and operations, and (vi) risks relating to legal and administrative proceedings.

Within each of these categories, these risks are ranked according to both their adverse effect and probability of occurrence, while taking into account the risk management measures adopted by the Company on the date of this universal registration document. The following table summarizes the key risks identified by the Company and indicates for each, the probability of their occurrence and their adverse effect on the Company on the filing date of this universal registration document. The probability of occurrence is ranked according to three classifications ("low", "moderate" and "high") and the severity of their adverse effect is ranked according to four classifications ("low", "moderate", "high" and "critical").

<b>Ref.</b>	<b>Risk factors</b>	<b>Probability</b>	<b>Adverse effect</b>
<b>3.1</b>	<b>Risks relating to the Company's financial position and capital requirements</b>		
3.1.1	Risks relating to cash burn which could impede or jeopardize the Company's continuing operations should it be unable to obtain the necessary financing	High	critical
3.1.2	Specific risks relating to the COVID-19 pandemic which could impact in particular the number of visits to doctors and therefore the amount of sales of VYZULTA and ZERVIAE, the recruitment of patients in clinical trials, and therefore the financial situation of the Society	High	critical



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<b>Ref.</b>	<b>Risk factors</b>	<b>Probability</b>	<b>Adverse effect</b>
3.1.3	Risks relating to the history of losses and the risk of future losses that have affected and may affect the financial position, cash flows and working capital of the Company and its ability to distribute dividends one day to its shareholders	High	High
3.1.4	Risks relating to commitments incurred in connection with bond financing obtained from Kreos Capital and loans guaranteed by the French State	Moderate	Critical
3.1.5	Risks associated with income and exchange rate fluctuations, reliability of investments	Moderate	High
3.1.6	Market risks	Low	Low
<b>3.2</b>	<b>Risks relating to products developed by the Company, regulatory authorizations and their commercialization</b>		
3.2.1	Specific risks relating to NCX 470 and NCX 4251 whose development cannot be guaranteed	High	critical
3.2.2	Specific risks relating to NCX 470, NCX 4251 and ZERVIAE development in Chinese region and other ex-China and ex-US geographies	High	critical
3.2.3	Risks relating to clinical and non-clinical trials affecting mainly NCX 470 and NCX 4251 which could significantly impact the Company's activity in the event of failure or delays	High	critical
3.2.4	Risks relating to new products whose development or sale could be disrupted impacting mainly VYZULTA and ZERVIAE and which could significantly affect the Company's outlook and financial position	High	critical



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<b>Ref.</b>	<b>Risk factors</b>	<b>Probability</b>	<b>Adverse effect</b>
3.2.5	Risks relating to competition and rapid technological developments which could render the products developed by the Company obsolete	High	critical
3.2.6	Uncertainty surrounding pricing and reimbursement schemes and reform of health insurance schemes	high	critical
3.2.7	Risks relating to the market launch of pharmaceutical products	moderate	critical
3.2.8	Risks relating to regulatory constraints which could impact the sale and or profitability of the Company's products, in the event of the refusal of an authorization or significant restrictions	moderate	critical
3.2.9	Specific risks relating to VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, commercialized by Bausch + Lomb, whose commercial success depends on a number of factors and remains uncertain	moderate	high
3.2.10	Specific risks relating to ZERVIA® (cetirizine ophthalmic solution), 0.24%, commercialized in the U.S. by Eyeavance Pharmaceuticals, whose commercial success depends on a number of factors and remains uncertain	moderate	moderate
3.2.11	Product liability and coverage from insurance policies	high	moderate
3.2.12	Environmental and industrial risks, financial risks linked to the effects of climate change	low	critical
<b>3.3</b>	<b>Risks relating to dependence on third parties</b>		
3.3.1	Dependence on third parties for carrying out clinical and non-clinical trials	high	critical



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<b>Ref.</b>	<b>Risk factors</b>	<b>Probability</b>	<b>Adverse effect</b>
3.3.2	Dependence on partners of collaboration agreements and outside consultants to effectively execute plans for development, obtain regulatory approvals and the marketing of products.	high	critical
3.3.3	Risks associated with manufacturers, the manufacturing costs of products, the price of raw materials and reliance on third party manufacturers	high	critical
<b>3.4</b>	<b>Risks relating to the Company's intellectual property</b>		
3.4.1	Infringement and potential infringement of patents and by other intellectual property rights covering our products and product candidates	moderate	critical
3.4.2	Scope, validity and enforceability of patents	moderate	critical
3.4.3	Litigation and defense of patent rights	moderate	critical
3.4.4	Possible infringements of third-party patents	moderate	critical
3.4.5	Products not protected by intellectual property rights, trade secrets for which the commercial potential could be affected	moderate	critical
3.4.6	Risk relating to the protection of trademarks the use of which could be subject to disputes	moderate	critical
3.4.7	Employees, consultants and subcontractors	moderate	critical
<b>3.5</b>	<b>Risks relating to the Company's organization, structure and operations</b>		
3.5.1	Reliance on qualified personnel	critical	critical
3.5.2	Risks associated with potential future acquisitions of products or companies and with potential future in-licensing transactions	moderate	moderate





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<b>Ref.</b>	<b>Risk factors</b>	<b>Probability</b>	<b>Adverse effect</b>
<b>3.6</b>	<b>Risks relating to legal and administrative proceedings</b>	moderate	moderate



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**3.1 Risks relating to the Company's financial position and capital requirements**

**3.1.1 Risks associated with cash burn**

At December 30, 2020, Nicox Group had cash and cash equivalents in the amount of €47.8 million compared to €28.0 million at December 31, 2019.

Based on a specific review of its liquidity risk, Nicox considers that on the date of this universal registration document the Company has sufficient net working capital to meet its cash requirements for the next twelve months and at least until the top-line results of the Mont Blanc Phase 3 clinical trial of NCX 470 expected in H1 2022 and therefore until the top-line results of the Mississippi Phase 2b clinical trial of NCX 4251 expected in Q4 2021.

Nicox anticipates significant capital requirements to complete the following projects:

- the development program for NCX 470 (a novel nitric oxide (NO)-donating prostaglandin analog based on Nicox's proprietary NO-donating research platform) for lowering of intra-ocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension;
- the development program for NCX 4251 (a novel patented ophthalmic suspension of fluticasone propionate nanocrystals) for acute exacerbations of blepharitis; and
- the early-stage development program focused on NCX 1728, the selected development drug candidate in a new class of NO-mediated IOP-lowering agents in preparation for pre-IND tests.

Developments and the cost of clinical and nonclinical trials, as well as costs relating to research and development programs, filing patents and concluding collaboration or product manufacturing agreements also give rise to significant capital requirements that must be met by Nicox.

To date, limited revenues are generated from royalties derived from the direct sales of products. Nicox expects sales for 2021 will not be sufficient to reach profitability. Furthermore, Nicox cannot guarantee that its choices in terms of cash utilization will prove appropriate. Nicox will need to raise additional funds in amounts that will depend on many factors, including the cost of developing or registering new products and, if appropriate, their commercialization. The Company might therefore have to seek other sources of funding:

- either through capital increases, it being specified that as a result of the volatility of the Nicox share price and constraints imposed in connection with capital increases entailing the cancellation of preferential subscription rights, this source of financing could be considered limited; or
- in the form of a debt; or
- by signing strategic partnership agreements with a view to generating new revenue from patent licenses, or to sharing operating costs with partners; or

Nicox cannot guarantee that its future capital requirements will be met or that additional funding will be available on acceptable terms. Turmoil affecting the stock markets has generally made it more difficult to obtain financing by equity securities and could have a materially adverse effect on Nicox's ability to obtain sufficient funding. If the Group were unable to obtain the necessary funding, it could be forced to delay, reduce or eliminate expenses related to certain projects that are under development, to seek funding



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through partnerships, to grant licenses for the development or marketing of products that the Group would have preferred to develop or market itself, which would have the effect of reducing the added value that the Group might ultimately draw from these products. Such a situation could even jeopardize the continuation of the Company's activities.

**3.1.2 Specific risks relating to the COVID-19 pandemic which could impact in particular the number of visits to doctors and therefore the amount of sales of VYZULTA and ZERVIAE, the recruitment of patients in clinical trials, and therefore the financial situation of the Society**

The sales of VYZULTA and ZERVIAE depend on the number of prescriptions which itself depends on the number of visits to doctors. A decrease in the number of visits would result in a decrease in the number of prescriptions and therefore a decrease in revenue for Nicox.

The duration and schedule of the Company's clinical trials depend on the number of patients recruited. If the recruitment is impacted by the COVID-19 pandemic and is no longer in line with the Company's estimates, the trials could take longer than expected and generate additional costs.

The coronavirus pandemic, as well as any other comparable health situation, can have a strong impact on the financial markets, on Nicox's share price, as well as on the Company's ability to finance itself and to advance its development programs on the expected timelines. This could have a significant negative effect on the Company, its business, financial situation and results, as well as on its development and prospects.

There is a risk that the COVID-19 pandemic will disrupt the activities of the Company, its partners and / or subcontractors and therefore have consequences on the development of its product candidates and on its funding needs.

**3.1.3 Risks relating to the history of losses and the risk of future losses that have affected and may affect the financial position, cash flows and working capital of the Company and its ability to distribute dividends one day to its shareholders**

To date, the Company has not yet generated significant revenues. The Company has not yet generated profit and has incurred operating losses each year since the commencement of its operations in 1996, and notably net losses for the periods ended December 31, 2019 and December 31, 2020 of (€18.9) million and (€18.1) million respectively.

Almost all the operating losses of the Company resulted from costs incurred in connection with research and development programs and the manufacture of products in preparation for their commercial launch, including activities in clinical and pre-clinical development phases, general and administrative costs linked to the Company's activities.

The payments that Nicox might receive from strategic partners under collaboration agreements might not be sufficient to cover its operating expenses and there is no guarantee, moreover, that the Group will receive additional payments under its collaboration agreements.



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Nicox may be expected to continue to incur significant expenses and its operating losses should increase in the near future as a consequence of the significant investments carried out in connection with the development of product candidates and the development of the selected candidate in a new class of NO-mediated IOP lowering agents.

These operating losses have had and may have a material unfavorable effect on the Company's financial position, cash flows and working capital. For that reason, no assurance can be given that the Company may one day be able to distribute dividends to its shareholders.

**3.1.4 Risks relating to commitments incurred in connection with bond financing obtained from Kreos Capital and and loans guaranteed by the French State**

Nicox has obtained financing of €20 million from Kreos Capital structured as bonds accessible as 3 tranches. The financing was structured into 3 tranches of senior secured bonds, the second tranche being divided into two sub-tranches. The first tranche of €8 million was drawn down on February 1st, 2019, the first sub-tranche of €4 million was paid on November 1st, 2019, the second sub-tranche of €3 million and the last tranche of €5 million were both drawn down on December 12, 2019 and paid on January 2, 2020. In January 2021 Nicox amended its bond financing agreement with Kreos Capital, introducing an additional one-year period of interest-only payments on the outstanding principal starting on February 1, 2021, and an extension of the overall period of the loan by 6 months to July 2024. The new one-year interest-only period is expected to provide approximately €5.5 million of additional flexibility for investment in development activities in 2021.

This financing includes standard early repayment clauses. A breach of Nicox's obligations under this contract could constitute a default event under these clauses and in consequence result in its early repayment. There can be no assurance that Nicox will have the resources required for the early repayment of this bond issue.

For additional information about the bond financing agreement with Kreos Capital, refer to section 20.2 of this universal registration document.

There can also be no assurance that cash flows generated by Nicox will be sufficient to pay the bonds at their maturity which could have a material adverse effect on its business, with security interests having been granted over certain tangible and intangible assets of Nicox S.A., and notably patents relating to the approved product VYZULTA (with the pledge having no impact on the exclusive worldwide license agreement with Bausch + Lomb), securities of the subsidiary Nicox Ophthalmics Inc. as well as a pledge of bank account balances and all receivables of more than €100,000.

In the third quarter 2020 we entered into a €2 million credit agreement, granted by Société Générale and LCL and guaranteed by the French State, in the context of the COVID-19 pandemic. This loan is not secured against any of the Company's assets. Up to 90% of the loan is guaranteed by the French State. It has an initial maturity of 12 months with the option for Nicox to take a 1 to 5-year repayment period after that.

**3.1.5 Risks associated with income and exchange rate fluctuations, reliability of investments**



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To date the Group's recurring revenue consist of royalties on sales of VYZULTA and ZERVIAE. The Group considers that there exists an uncertainty about the evolution and stability of this revenue which could potentially impact its sources of funds.

The majority of the Group's expenses are denominated in US dollars. In fiscal year 2020, approximately 55.8% of operating expenses were in US dollars (47.9% in 2019).

Foreign exchange fluctuations in the value of the euro in relation to the US dollar may result in a material impact on the Group's operating results, notably with respect to the worldwide license for VYZULTA granted to Bausch + Lomb and, license for ZERVIAE for the U.S. market granted to Eyeavance for which the Group may receive milestone payments respectively for an amount of up to US\$165 million for VYZULTA and \$37.5 million for Eyeavance in addition to up 6% to 12% in net royalties for VYZULTA and to up 8% to 15% for ZERVIAE.

The Group does not have significant receivables subject to foreign exchange risks.

The Group also holds US dollar bank accounts that are translated into euros in the consolidated financial statements at the year-end exchange rate. Cash amounted to €12 713 000 at December 31, 2020 (or 27% of cash and cash equivalents) and may be materially impacted by the Euro/US Dollar exchange rates. This risk is however mitigated by the fact that cash is exclusively destined to cover the Group's expenses denominated in US dollars resulting from its research and development activities in the United States over the medium term.

**3.1.6 Market risks**

For additional information, refer to note 25.3 "Market risk" to the consolidated financial statements for the period ended December 31, 2020.

**3.2 Risks relating to products developed by the Company, regulatory authorizations and their commercialization**

**3.2.1 Specific risks relating to NCX 470 and NCX 4251 whose development cannot be guaranteed**

NCX 470 is a novel nitric oxide (NO)-donating prostaglandin analog in development for the lowering of IOP in patients with open-angle glaucoma and ocular hypertension. Another Nicox product candidate, which leverages an established molecule, is NCX 4251, a novel patented ophthalmic suspension of fluticasone propionate nanocrystals which is being developed as a targeted topical treatment of the eyelid for patients with acute exacerbations of blepharitis. NCX 4251 has also shown a potential for development in dry eye disease.

The Company has completed a Phase 2 clinical trial, Dolomites, for NCX 470. The first Phase 3 clinical trial, Mont Blanc, necessary for U.S. regulatory approval was initiated in the U.S. on June 1<sup>st</sup> 2020 following a successful End-of-Phase 2 meeting with the FDA. The second Phase 3 clinical trial, Denali, was initiated on November 9<sup>th</sup>, 2020 and, together with the Mont Blanc trial, is designed to fulfill the



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regulatory requirements for Phase 3 safety and efficacy trials to support New Drug Application (NDA) filings of NCX 470 both in the U.S. and China. The Denali trial will be financed jointly and in equal parts by Nicox and our Chinese partner Ocumension and will include clinical sites in both the U.S. and China, with a majority of the patients in the trial to be recruited in the U.S. The management of a multi-country clinical trial is more complex than in one country alone. The Denali trial includes a long-term safety extension. Certain additional clinical and non-clinical data will be required to support NDA submissions. The requirements for a Chinese NDA submission may be different from those in the U.S.

The Company has also completed a Phase 2 clinical trial of NCX 4251, Danube. A Phase 2b and at least one Phase 3 clinical trial, long term safety data and certain additional clinical and non-clinical data, will be necessary to support an NDA submission in the United States. The requirements for a Chinese NDA submission may be different from those in the U.S. A Phase 2b clinical trial, Mississippi, was initiated in the U.S. on December 14<sup>th</sup>, 2020 for the treatment of acute exacerbations of blepharitis. If successful in meeting the primary endpoint previously agreed upon with the FDA, the trial could represent the first of two pivotal trials needed to support an NDA in the U.S.

There is a risk that the results of these trials may not be sufficient to move forward with the development of these products or that additional trials prove necessary to advance their development or in order to file for approval to commercialize NCX 470 or NCX 4251. Trials may be more costly or longer than expected. There is no guarantee that Nicox can file an NDA in the United States for NCX 470 or NCX 4251 in the future.

The development of NCX 470 and NCX 4251 could be delayed or fail.

**3.2.2 Specific risks relating to NCX 470, NCX 4251 and ZERVIA development in ex-US and ex-China geographies**

The Company has multiple collaborations concerning the development and commercialization of its products and product candidates in countries outside of the U. S. and China, and expects to enter into further collaborations in the future. The regulatory requirements in such countries may be different from those in the U.S. and China. If additional clinical or nonclinical studies are required, the Company or its partners may have difficulty finding suitable local contractors.

The development plans for product candidates are currently focused on obtaining regulatory approval in the U.S. initially, and in China for NCX 470. Other countries may require additional clinical or non-clinical data to support regulatory approval, which may delay development and launch in those countries. Generating additional data or incorporating the regulatory requirements of those countries into the Company's development plans may results in delay to, or increase the risk of, the development of such product candidates in those countries.

For products which have been approved in the U.S., the FDA approval may, in some cases, be used as a basis for regulatory approval outside of the U.S. However, there is no guarantee that such regulatory approval will be achieved without generation of additional clinical or non-clinical data, or that the product approved in the U.S. will be approved outside of the U.S.





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**3.2.3 Risks associated with clinical and non-clinical trials**

It cannot be guaranteed that the necessary authorizations will be obtained to conduct clinical trials.

There can be no assurance that the authorized trials will be conducted in a timely manner or that they can be conducted without significant additional resources or knowledge. Significant delays in the conduct of clinical and non-clinical trials could generate additional costs in connection with the development of the drug candidates in question. Such delays could also limit the period of exclusivity available to Nicox to commercialize its drug candidates.

Pharmaceutical companies or the regulatory authorities may suspend or terminate clinical trials if they consider that the trial patients are exposed to health risks.

The conduct of clinical trials depends on various factors such as indication, size of the affected population, nature of the clinical protocols followed, proximity between patients and clinical trial sites, eligibility criteria for trials, competition from other companies for the enrollment of patients to conduct clinical trials, availability of sufficient amounts of a compound of appropriate quality, ability to enter into agreements with appropriate subcontractors (and the discharge by them of their contractual obligations), and compliance with the regulatory standards.

The product candidates under development may not have the desired effects or may cause adverse reactions that preclude regulatory approval or limit their marketing. It frequently occurs that the favorable results of non-clinical studies and preliminary clinical trials are not confirmed in subsequent clinical trials.

Clinical trials may produce insufficient data to obtain regulatory approval.

This risk concerns mainly NCX 470 and NCX 4251 which are currently under clinical development. The risks related to the development of NCX 470 and NCX 4251 may be different for the ex-US and ex-Chinese region.

While VYZULTA and ZERVIAE have been approved in selected territories, they remain subject to risks relating to clinical development in those territories where a marketing authorization is required which remains contingent on the nature of requirements imposed by regulatory authorities in these territories.

For additional information, refer to Section 3.1 of this universal registration document.

**3.2.4 Risks relating to new products**

The development or sale of new products generates risks associated with their novelty.

New Molecular Entities (NMEs) are compounds whose chemical and pharmacological profile is unknown at the time of their discovery. The product candidates under development covered by patents filed by Nicox relating to our nitric oxide release (NO) technology are NMEs. Each NME must be subjected to studies or extensive testing so that its chemical and pharmacological properties can be studied and investigated in detail. The outcome of these studies can entail a degree of uncertainty. Consequently, there



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can be no assurance that these compounds will demonstrate the same chemical and pharmacological properties in patients as those observed in the preliminary laboratory and animal studies, nor that these compounds will not interact unpredictably and toxically with human biological functions. NCX 470 is a product candidate containing an NME.

When a molecule achieves first regulatory approval, it may be considered a New Chemical Entity (NCE). This classification allows for certain additional periods of marketing or patent exclusivity. We believe NCX 470 is a product candidate containing an NCE, however the classification is made upon regulatory approval and there is no guarantee that such NCE status will be granted.

As new compounds, given that the uncertainties of their development, manufacture and properties are not known at the time of their design, difficulties may arise which might cause the company to terminate their development or their sale, thereby potentially affecting the company's prospects or financial position.

Certain product candidates under development by Nicox may include molecules that have already been approved. If the development data relating to the previous development of these molecules is available, Nicox may use it, but there is a risk that a molecule used in another formulation or for another indication or for another route of administration will present different side effects. Additional safety studies and/or efficacy studies on the new indication or formulation or route of administration may be required. NCX 4251 is a product candidate containing a molecule which has already been approved.

**3.2.5 Risks relating to competition and rapid technological developments**

The markets in which Nicox operates are highly competitive and rapidly changing. The Company competes with larger companies with development programs that target the same indications, and with greater experience in the development and marketing of products. In addition, these companies have far greater financial and human resources than the Company. As a result, the Company cannot guarantee that its products:

- Will be able to obtain the required regulatory approval or be brought to market more quickly than those of its competitors;
- Will be able to compete with safer, more effective or less expensive existing or future products;
- Will adapt quickly enough to new technologies and scientific progress; and
- Will be accepted and selected by medical centers, physicians or patients to replace existing products.

New developments are expected both in the healthcare industry and in public and private research facilities. In addition to the development of safer, more effective and less costly products than those developed or marketed by Nicox, its competitors may manufacture and market products under better conditions. Furthermore, competitors' rapid technology developments may render products of the





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Company obsolete before Nicox is able make the costs of research, development, acquisitions/licenses and marketing.

**3.2.6 Uncertainty surrounding pricing and reimbursement schemes and reform of health insurance schemes**

The ability of Nicox and its partners to secure commercially viable prices for its products that may potentially be marketed in the future depends on several factors, including the profile of its product compared to that of its competitors' products, the price of competing products, the existence of generic products and the targeted geographic area. The Company cannot guarantee that its products will secure pricing agreements for cost-effective marketing within the broader context, where pressure on pricing and reimbursement intensifies (greater control over prices, increased delisting, trend towards the promotion of generics).

In fact, the commercial success of the Group's products depends in part on the agreement of the regulatory authorities responsible for health insurance, private insurance companies and other similar organizations in terms of product prices and reimbursement rates. Governments and third-party payers seek to control public health expenditure by limiting the reimbursement of new products. The Group cannot guarantee that it, its partners or its distributors will obtain a high enough reimbursement rate or price for the Company's products and the commercial profitability of these products in the market may consequently be affected.

In addition, pricing and prescribing freedom in some markets are governed and limited by the public authorities. The introduction of more stringent controls on pharmaceutical pricing can have a negative impact on the company's activities, either directly on the products it intends to sell or indirectly on the amount of income that the company can earn through its partnerships and licensing agreements.

**3.2.7 Risks relating to the market launch of pharmaceutical products**

The market launch of pharmaceutical products of the Company is subject to the following risks which could seriously affect the Company's financial position and prospects:

- Regulatory approvals, including of marketing materials and branding, may not be granted in time to secure a commercial return;
- The products may be difficult to produce on an industrial scale or their production on an industrial scale may prove too expensive;
- The products may not be profitable because of their cost of production, distribution and/or sale price as imposed by the relevant regulatory authorities;
- The products may not qualify for reimbursement arrangements in some countries, thereby jeopardizing their commercial potential in certain jurisdictions;
- It may be difficult to achieve acceptable quality standards;



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- The company may not find a trading partner for the marketing of its products;
- The products may not be marketable on account of rights held by third parties;
- Third parties may market similar products that offer a higher benefit-risk ratio or a more competitive price; and
- A secondary effect or a manufacturing quality problem may arise at any time for a marketed product, which could lead to the restriction or withdrawal of regulatory authorizations for this product.

A pharmaceutical product can only be introduced on the market only after it has successfully completed all phases of development provided for by regulations in force in the territory in question. This risk concerns, in the short term, VYZULTA and ZERVIAE. Specifically, VYZULTA is currently being commercialized by partner Bausch+Lomb in the United States, Canada, Mexico and Argentina, and has been approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine. However, no assurance can be given that the product will be marketed in other territories. While ZERVIAE has been commercialized in the United States by U.S. partner EyeVance Pharmaceuticals since March 2020, it is possible that ZERVIAE might never be marketed in other territories. With respect to the other product candidates, the risk associated with marketing will persist until a future date in light of their current stage of development.

**3.2.8 Risks relating to regulatory constraints**

The regulatory process may give rise to delays or rejections. The U.S. and European, regulatory authorities tend to impose ever more cumbersome requirements, particularly regarding the volume of data required to demonstrate safety and efficacy. Other regulatory authorities, including China, may also change their requirements for the approval of pharmaceutical products.

Pharmaceutical products cannot be marketed in a given jurisdiction until they have been approved by the relevant regulatory authority, and all pharmaceutical development requires non-clinical and clinical trials to demonstrate the safety and efficacy of the compound under evaluation. The unfavorable outcome of clinical trials or applications for regulatory approval of the therapeutic products developed by the Group is likely to have a material adverse effect on its business.

The achievement of primary endpoints of clinical trials, even with statistically significant results, does not guarantee that the drug-candidate will then be approved by the regulatory authorities. Those authorities may argue that the comparator was inadequate, that the number of patients involved was insufficient, or that the results, although statistically significant, are not clinically significant.

Even after they have been approved, drugs and their manufacturers are subject to continuous and permanent review and the uncovering of problems or the inability to comply with the manufacturing and quality control requirements may lead to restrictions in the distribution, sale or use of these products and even to their withdrawal from the market.



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The regulatory authorities have the authority, when approving a product, to impose significant limitations on the product in the form of warnings, precautions and contraindications, or restrictions on the indicated use, conditions for use, labeling, advertising, promotion, marketing, distribution and/or production of the product that could negatively affect its profitability.

The EMA, the U.S. FDA, the Chinese NMPA and similar regulatory bodies may also implement new standards, or change their interpretation and enforcement of existing standards and requirements, for the manufacture, packaging or testing of products at any time. A company that is unable to comply could be subject to regulatory or civil proceedings or be ordered to pay fines.

New regulations may be enacted. Given the disparity of the regulations and procedures, which vary from one country or jurisdiction to another, obtaining authorization in each country within a reasonable time frame cannot be guaranteed.

As part of its research and development work Nicox is, or may be, subject to regulations concerning safety standards, good laboratory practice (GLP), good clinical practice (GCP), good manufacturing practice (GMP), the experimental use of animals, the use and destruction of hazardous substances, in addition to regulations and market surveillance good practice (including medical device vigilance and pharmacovigilance) where the products are marketed. In the event of non-compliance with the applicable regulations, the company may be subject to penalties which may take the form of temporary or permanent suspension of operations, withdrawal of the product, restrictions on the marketing of the product and civil and criminal penalties.

**3.2.9 Specific risks related to VYZULTA® (latanoprostene bunod ophthalmic solution),  
0.024%**

VYZULTA® is a prostaglandin analog with one of its metabolites being NO. VYZULTA was developed for the reduction of IOP in patients with open angle glaucoma or ocular hypertension. The marketing authorization application for VYZULTA, submitted by its exclusive licensee, Bausch + Lomb (a company of Bausch Health Companies, Inc.) was approved by the U.S. FDA in November 2017 and VYZULTA has been marketed in the United States by the licensee since December 2017. VYZULTA is also approved and commercialized in Canada, Mexico and Argentina and has been approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine.

The Company has identified the main risks related to VYZULTA below. Moreover, it should be noted that all of the “Risks related to Nicox’s strategy and business: the research, development and marketing of ophthalmic products” apply to VYZULTA.

Outside the United States, Canada, Argentina, Colombia, Mexico, Hong Kong, South Korea, Taiwan and Ukraine, it is still necessary to obtain regulatory approvals before launching VYZULTA on the market. There is no guarantee that Bausch + Lomb will file an application for countries other than the United States, Canada, Argentina, Colombia, Mexico, Hong Kong, South Korea, Taiwan and Ukraine or that if such applications are filed, that they will be successful.



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As for marketing authorizations in Europe, a marketing authorization application (MAA) must be filed with the EMA (European Medicines Agency) or – in accordance with the decentralized procedure – with the national regulatory authorities of the European countries covered, which would conduct a validation process and scientific approval to evaluate the safety and efficacy of the drug.

The requirements of the EMA or national regulatory authorities may differ significantly from those of the U.S. FDA and these authorities may request the conduct of different non-clinical and clinical studies.

***If VYZULTA has limited or no commercial potential, the Group's activities could be harmed***

Nicox is contractually entitled to receive from Bausch + Lomb net royalties on sales of 6 % to 12 % after deduction of payments owed to Pfizer (see Section 5.2.1 for additional information concerning these payments). Royalties received by Nicox depend on sales generated by Bausch + Lomb, which depend on the commercial success of VYZULTA in the United States, Canada, Argentina, Colombia, Mexico, Hong Kong, South Korea, Taiwan and Ukraine and any other territories where it may be commercialized. Nicox cannot guarantee such commercial success. Figures for actual sales may be impacted by the following factors:

- The commercial success of VYZULTA depends on several factors (none of these factors can be guaranteed by the Group), including:
  - Bausch + Lomb's success in obtaining a satisfactory product reimbursement level and sale price after, as applicable, discounts, allowing for viable business development;
  - The maintenance and development of commercial production capabilities at Bausch + Lomb that provide for flexible conditions to ensure enough orders are processed;
  - VYZULTA's acceptance by the medical community, and, more generally, the success of its launch, commercial sales and distribution.
  - Bausch + Lomb's continued ability to manufacture VYZULTA in accordance with applicable regulatory requirements; and
  - Bausch + Lomb's ability to obtain marketing approvals in other countries for VYZULTA and its wish to apply for such authorizations.
- In addition, restrictions on the use, promotion or sale of VYZULTA or other post-approval restrictions could limit the market potential and reduce the sales volume of the product and its profitability;

Bausch + Lomb has focused its efforts on the United States and countries which accept U.S. FDA approval or reference to existing studies in support of marketing applications in local countries. To our knowledge, marketing applications have not been filed in Europe or Japan and we are not aware of any such plans. In addition, no assurances can be given that such marketing authorizations would be approved.



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The absence of a marketing authorization for VYZULTA outside the United States, Canada, Argentina, Colombia, Mexico, Hong Kong, South Korea, Taiwan and Ukraine could limit the commercial success of this product and have a significant effect on the Company's financial position and delay achieving its objectives.

Bausch Health Companies, Inc., has announced their intention to create a spin-off company around Bausch + Lomb. There is a risk this may impact sales of VYZULTA.

**3.2.10 Specific risks related to ZERVIA<sup>®</sup> (cetirizine ophthalmic solution), 0.24%**

ZERVIA<sup>®</sup> is an innovative and patented cetirizine-based eye-drop developed to treat ocular itching (itchy eyes) associated with allergic conjunctivitis. In May 2017, the NDA for ZERVIA for the United States was approved by the U.S. FDA.

The Company has identified the main specific risks associated with ZERVIA and has listed them below.

***If ZERVIA has limited or no commercial potential, the Group's activities could be harmed***

In September 2017, Nicox entered into an exclusive license agreement with Eyevance Pharmaceuticals for the commercialization of ZERVIA in the United States. All manufacturing and regulatory responsibilities, together with decisions on launch timing, lie with Eyevance. Eyevance launched ZERVIA in a unit-dose presentation in the U.S. in March 2020 and expects a multi-dose presentation in the future. Many countries outside of the U.S. and other major markets base their regulatory approval on FDA approvals. Consequently, the development programs outside of the U.S. may be negatively impacted by the delayed availability of the multi-dose trade unit product presentation and their development risks may increase.

In March 2019, the Company entered into an exclusive license agreement with Ocumension Therapeutics for the development and commercialization of ZERVIA for a territory comprising mainland China, Hong Kong, Macau and Taiwan or the Chinese market. In March 2020 the license agreement was amended to expand Ocumension exclusive rights to the majority of the Southeastern Asian countries.

In December 2019, the Company entered into an exclusive license agreement with Samil Pharmaceutical for the development and commercialization of ZERVIA in South Korea.

In August 2020 the Company entered into an exclusive license agreement with ITROM Pharmaceutical Group for the development and commercialization in Gulf and Arab markets.

No guarantee exists that the Company or its partners will obtain regulatory authorizations to sell ZERVIA outside the United States.

The Company cannot guarantee such commercial success.



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- Regulatory authorities might impose restrictions on the use or sale of ZERViate. These restrictions could limit the potential market, delay the launch and/or reduce the level of sales and profitability of the product.
- The commercial success of ZERViate will depend on several factors (none of which can be guaranteed by the Group), including:
  - Availability of the product within the timeframe and in sufficient quantities to support the commercial launch;
  - EyeVance's success in obtaining a satisfactory reimbursement level and sale price after, as applicable, discounts, allowing for viable business development;
  - The maintenance and development of commercial production capacities that provide for flexible conditions to ensure enough orders are processed;
  - The Company's ability to include new partnerships to develop and market ZERViate in other countries;
  - The ability of our partners to obtain regulatory authorizations in other countries; and
  - The acceptance of ZERViate by the medical community, and, more generally, the success of the launch, commercial sales and distribution.
  - EyeVance was acquired by Santen Pharmaceutical Co., Ltd of Japan in September 2020. There is a risk this may impact sales of ZERViate.

**3.2.11 Product liability and coverage from insurance policies**

The use of product candidates under development in clinical trials and the possible sale of drugs may expose the company to liability suits. In the United States, the approval of a product by the U.S. FDA may only offer limited or indeed no protection against liability claims based on federal state law (federal preemption cannot be invoked), and the obligations imposed on the company may vary from one federal state to another. If the company cannot successfully defend against liability suits, including liability in connection with clinical trials of its product candidates under development or with future commercial sales of its therapeutic products under development, it could incur heavy liability with potentially adverse consequences for the company.

The insurance policies obtained by the Company might not adequately cover the risks of its existing activities.

Whatever the grounds or eventual outcome of any liability suits, they could result in a fall in demand for a product, a reputation loss for the company, the withdrawal of volunteers from clinical trials, the withdrawal of a product from the market and/or loss of revenue.





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**3.2.12 Environmental and industrial risks, financial risks linked to the effects of climate change**

Nicox's research and development activities involve the storage, use and disposal of hazardous radioactive and biological products (see Section 5.6.3 of the 2019 Universal Registration Document). Since 2012, these activities have been outsourced. Although these activities are monitored and involve only small amounts of hazardous materials, they pose a risk of contamination to the environment. Even though the Group believes that its activities and procedures comply with standards laid down by applicable laws and regulations, the risk of accidental contamination or injury due to the storage, use and disposal of these hazardous materials cannot be completely eliminated. Nicox could therefore be held liable for amounts over and above the limits of its insurance policy (see Section 3.7.1 of this universal registration document). The occurrence of such a risk could have a significant negative impact on the Group's financial position.

The Company has not identified any specific risk, in particular financial, linked to the effects of climate change and has therefore not taken any action in this regard, which does not mean that this risk does not exist.

**3.3 Risks relating to dependence on third parties**

**3.3.1 Dependence on third parties for carrying out clinical and non-clinical trials**

The Company has recourse to subcontractors, and in particular medical institutions, clinical researchers, clinical research organizations to conduct its clinical and non-clinical trials. The Company is able to exercise full control over the activity of its subcontractors.

Should its subcontractors fail to respect the terms of their engagement or not succeed in meeting the deadlines provided for within the framework of the trials to be conducted, the Company might be required to delay the development and sale of certain drug candidates.

In the event of default by subcontractors responsible for conducting clinical and non-clinical trials, no assurance can be given that the Company will find an alternative solution with other parties which offer acceptable commercial conditions.

In consequence, the occurrence of one or more of these risks could have a material adverse effect on the Group's business, financial position and prospects.

**3.3.2 Dependence on partners of collaboration agreements and on outside consultants**

To maximize its chances of success to launch its products on the market, it could be preferable for Nicox to enter into collaboration agreements with third party companies, and notably Bausch + Lomb for VYZULTA, Eyeavance Pharmaceuticals, Samil Pharmaceutical and ITROM Pharmaceutical Group for ZERVIAE, and Ocumension Therapeutics for ZERVIAE, NCX 4251 and NCX 470. The



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Company cannot guarantee that it will be able to maintain the collaboration agreements in force, enter into new agreements in future on acceptable terms, or that these agreements will produce the desired results.

When the Company enters into a collaboration agreement, it runs the risk that its partner may unilaterally and arbitrarily terminate the agreement or decide not to market the product. If current partners decided to terminate the agreements in place, or the development of selected compounds, the Company would then have to pursue the development of these products itself, seek new partners or cease their development. Such a situation could increase the company's costs and/or adversely affect its business. The termination or non-renewal of a collaboration agreement could also adversely affect the Company's image and share price.

Conflicts could arise with the company's partners. In addition, the Company's partners could seek to compete with it. The existence of non-competition clauses in the company's collaboration agreements may not provide adequate protection.

Nicox also relies on outside consultants and subcontractors (such as academic researchers, medical specialists, and clinical and pre-clinical research organizations) to develop its products. Agreements between the company and such consultants and subcontractors may include limitation of liability clauses in favor of the other contracting party, in which case the company may not be able to secure full compensation for any losses incurred if the other contracting party fails to perform. Competition for access to these consultants is high, and the company cannot guarantee that it will be able to maintain its existing relationships on commercially acceptable terms. In general, contracting parties may terminate the contract at any time.

The Company depends on the successful execution by its partner licensees of the development plans, regulatory submissions and for obtaining regulatory and marketing approvals for the products. In consequence, the occurrence of one or more of these risks could have a material adverse effect on the Group's business, financial position and prospects.

**3.3.3 Risks associated with manufacturers, the manufacturing costs of products, the price of raw materials and reliance on third party manufacturers**

Because Nicox's products and drug candidates are manufactured by third parties, it has limited control over manufacturing activities. Nicox has neither the infrastructure nor the experience required to manufacture pharmaceutical products. Nicox's dependency vis-à-vis third parties and its lack of experience in commercial-scale production increases the risk of difficulties or delays since its drug candidates are manufactured by third-party manufacturers, for clinical and non-clinical trials, but also for sale after the products have been approved. Unforeseen manufacturing problems could cause delays in commercial sourcing or the clinical trials.

The manufacture of VYZULTA is the responsibility of Bausch + Lomb worldwide.

The manufacture of ZERVIAE for the U.S. is the responsibility of Eyevance. However, in countries whose regulatory approval depends, or will depend, on the U.S. FDA approval of ZERVIAE, any





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changes in the approval and status of manufacturing may negatively impact Nicox's development partners and programs in such country. In some cases, a different manufacturer or product presentation may also be required by Nicox's partners. In such case, transfer of manufacturing may result in delays to regulatory approval.

Any decision by the manufacturers to alter the price of the products could negatively affect the margin received by Nicox. Nicox might delay the development or marketing of its products under development if their manufacture is disrupted or stopped.

The manufacture of medicines must comply with the applicable regulations and with good manufacturing practices, which is a complex, time-consuming and expensive process. Manufacturers may be subject to inspections prior to approval by regulatory authorities before obtaining marketing authorizations. Even after product approval, the facilities of manufacturers with whom the Company is associated are subject to periodic inspections by regulatory authorities or administrative authorizations that may be suspended. Nicox cannot guarantee that such inspections would not give rise to compliance issues that may prevent or delay marketing authorization, adversely impact the Group's ability to retain approval of the product or its distribution, or oblige the Group to use additional resources, financial or otherwise. Business would be negatively affected should its manufacturers fail to comply with the applicable regulations and recommendations.

A higher than anticipated cost of manufacturing the products or a significant rise in the cost of the raw materials needed for their manufacture could affect the commercial prospects of these products or the Group's margin. In these circumstances, the Group may have to halt the development or sale of these products, thereby potentially affecting the Group's financial position or prospects.

In addition, the Group's ability to develop and deliver products in a timely and competitive manner could be significantly affected if, for example, the Group is unable to maintain relations with manufacturers possessing the requisite facilities and expertise, if contract disputes arise, or if other events hinder production.

### **3.4 Risks relating to the Company's intellectual property**

#### **3.4.1 Infringement and potential infringement of patents and by other intellectual property rights covering our products and product candidates**

The Company, by the nature of its activity, is highly dependent on the protection of its intellectual property.

As far as patent-protected products are concerned, if the patent or patents relating to a product developed, in-licensed or acquired by the company were invalidated or declared unenforceable, the development and marketing of such compound or product would be directly affected or interrupted. The company may, for budgetary or other reasons, not be able to retain its patent portfolio in full, given the high cost of annuities and of potential lawsuits.

Nicox cannot therefore guarantee that:



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- It will develop new patentable inventions, or that its patents will allow it to develop commercially profitable products;
- The filed patent applications will be granted;
- If these patents are granted, they will not be challenged, invalidated or declared unenforceable;
- That third parties will not develop products that are not in the scope of protection of its patents; or
- The products that it develops or might in-license or acquire will not infringe, or will not be alleged to infringe, patents or other intellectual property rights owned by third parties.

#### **3.4.2 Scope, validity and enforceability of patents**

The grant of a patent does not guarantee its validity or its enforceability and may not provide exclusive protection or competitive advantages against competitors with similar products.

To ensure the longest possible exclusivity, the company intends to seek an extension of certain of its patents for a period of up to 5 years. Nevertheless, it cannot guarantee that such extensions will be obtained and failure to obtain these extensions is likely to harm the products concerned. The portfolio of patents and patent applications of the Company covers a number of products. The failure to obtain an extension for patents could have a significant impact for the sale of products concerned and expose the Company to increased competition, which would have consequences on the Company's financial position and prospects.

In particular, the expiration of patents protecting VYZULTA (protection in the United States until 2025, which may be subject to extension to 2030), ZERVIAE (protection aux in the United States until 2030 and 2032), NCX 470 (protection in the United States until 2029 under a composition of matter patent and for the formulation patent until 2039), and NCX 4251 (protection in the United States by a patent expiring in 2033) could have a material adverse effect on the Company's business and financial position (for additional information, refer to Sections 5 and 7 of this universal registration document).

#### **3.4.3 Litigation and defense of patent rights**

Competitors can or could infringe the patents of products developed or marketed by Nicox or attempt to circumvent them. The company may have to resort to legal action to enforce its rights, to protect its trade secrets or to determine the scope and validity of others' proprietary rights. Furthermore, the ability of the Group to assert its rights under patents depends on its ability to detect infringements. It is difficult to detect infringers who do not advertise the compounds used in their products.

The protection conferred by a patent in practice varies by product and by country, and depends on many factors such as the nature of the patent, the scope of its protection, the possibility of regulatory extensions, the existence of legal remedies in a given country, and the validity and enforceability of the patents. The



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laws governing patents are constantly changing and vary from one country to another, with potential for rendering protection uncertain. The Company's patent portfolio includes patents issued in various foreign countries which are on that basis at particular risk.

Any litigation to assert or defend the Group's rights under patents, even if the rights of the Company should prevail, may prove costly in resources and time, and would divert the attention of management teams and key employees from carrying out Company business, which could have a material adverse effect on the Company's operations.

**3.4.4 Possible infringements of third-party patents**

Products developed or in-licensed by the company must not infringe the exclusive rights belonging to third parties. Third parties may also allege infringement by Nicox of their patents or of other intellectual property rights (see Section 3.6 "Risks relating to legal and administrative proceedings"). If a legal action is brought against the company on such grounds, there can be no assurance that the company will win the case. Moreover, even if Nicox conducted prior art searches to determine whether its rights infringe the rights held by third parties, it cannot be certain that all relevant rights have been identified because of the uncertainty inherent in this type of search. Such disputes could divert the attention of management teams and key personnel from their task of managing the Company's operations which could have a material adverse effect on the Company's business.

Any claim of patent infringement whose outcome is unfavorable to Nicox could require it to pay significant damages as well as royalties. As a result of claims by third parties, the company may be forced to change or rename its products to avoid infringement of the intellectual property rights of third parties, which could prove either impossible or costly in resources and time. In these circumstances, the Group may have to halt the development and/or sale of these products which may have adverse effects on the Company's financial condition and prospects.

**3.4.5 Products not protected by intellectual property rights; trade secrets;**

The Company may be required in connection with its activities to license or sell therapeutics that are not protected, in all or part of the territories concerned, by intellectual property rights. In this case, it is likely that other market participants will market similar or identical products on the same markets, which may seriously affect the commercial prospects of such products as a result of this increased competition, or indeed the financial condition of the Company.

The development new therapies by the Company depends in part on protecting trade secrets in order to preserve the confidentiality of technologies and processes used. Where there exists non-public know-how or other trade secrets concerning a product (whether or not the product is patent-protected), the company cannot be certain that confidentiality will be ensured and that such know-how or trade secrets will not be disclosed. If disclosed, the products covered by such trade secrets could see their commercial potential diminished.

**3.4.6 Risks relating to the protection of trademarks**



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Nicox is exposed to certain risks related to trademarks. Nicox has submitted applications in numerous countries in order to register several trademarks, particularly for its products. These trademark applications may not result in registration or may be canceled following their registration on the grounds of non-use, revocation or infringement. The company may be denied use of the brand name. Some trademark applications filed by the company may be subject to opposition proceedings. There is no guarantee that the company will be able to resolve these trademark-related disputes and similar disputes in the future. Also, trademarks intended to designate products may be rejected by the relevant regulatory authorities.

#### **3.4.7 Employees, consultants and subcontractors**

The company cannot guarantee that the confidentiality agreements signed with its employees, consultants and subcontractors will be respected, that it will have adequate remedies for disclosure of confidential information, or that sensitive data will not be brought to the knowledge of third parties in another manner or independently developed by competitors.

Nicox regularly enters into agreements with researchers working in academia or with other public or private entities and, in such cases, the company has entered into intellectual property agreements with these entities. However, the company cannot guarantee that these entities will not claim intellectual property rights over the results of work conducted by their researchers, or that they will grant licenses for such rights to the company on acceptable terms. This would have a significant adverse impact on the company's business and financial condition.

### **3.5 Risks relating to the Company's organization, structure and operations**

#### **3.5.1 Reliance on qualified personnel**

The company's activities rely on a number of key managers and scientists, including particularly members of the Executive Committee. Competition for the recruitment of managers and qualified personnel is fierce in the Group's area of activity. The Group's strategy for development and expansion requires the continuing expansion of teams by recruiting qualified personnel. The Group cannot guarantee that it will be able to retain the human resources currently available to it or that it will be able to recruit any new resources it might require. The departure of key managers or scientists could delay the achievement of objectives in terms of research and development and the commercialization of products, which would significantly impact the Group's business and prospects.

In addition, the Group's limited workforce does not allow for replacements in the case of the absence of an employee so that the prolonged leave of an employee can significantly disrupt operations.

#### **3.5.2 Risks associated with potential future acquisitions of products or companies and with potential future in-licensing transactions**

In response to competition and the increasing concentration of resources in the pharmaceutical industry, the Group has carried out and will continue to carry out acquisitions. In addition to the portfolio of assets developed in-house, the Group could acquire rights to product candidates through in-licensing



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transactions, at different stages of advancement. The Group might however be unable to identify appropriate acquisition targets or conduct acquisitions under acceptable terms or could even find itself unable to complete the integration of these acquisitions, which would be likely to disrupt Group operations and have a negative impact on its activities and its results.

Nicox might continue to seek acquisitions with the aim of optimizing its business model, developing its customer base, accessing new markets and achieving economies of scale. Acquisitions entail certain known and unknown risks that could mean that the Group's growth and actual operating results differ from its forecasts. Thus, the Group:

- might not manage to identify suitable acquisition targets under acceptable terms;
- might seek acquisitions in foreign countries, which represents greater risks than those inherent to domestic acquisitions;
- might find itself in competition with other companies for acquiring complementary products and activities, which could be reflected by lesser availability or an increase in the acquisition costs of intended targets;
- might not achieve the necessary financing under favorable terms, or not achieve any financing at all, for all or some of the potential acquisitions; or
- the products or activities acquired might not generate results in line with the Group's forecasts, which would then risk not achieving the anticipated revenue and returns.

Furthermore, such an acquisition strategy could divert Management's attention from its existing activities, resulting in a loss of key employees. This strategy could also expose the management to unexpected problems or liabilities, such as successor liability for contingent or undisclosed liabilities related to the activities or assets acquired.

If the Group fails to conduct effective prior assessment of these potential targets (due diligence), it risks, for example, to not identify the problems of target companies or not identify incompatibilities or other obstacles to successful integration. Its inability to integrate future acquisitions satisfactorily could prevent it from receiving all the benefits of these acquisitions and considerably weaken its operational activities. The process of integration may also disrupt its activity and, if new products or activities are not implemented effectively, prevent the Group from fully achieving the expected returns and prejudice its operating results. Furthermore, the total integration of new products or new activities may cause unexpected problems, expenses, liabilities and reactions from the competition. Difficulties related to the integration of an acquisition include the following:

- difficulties in integrating products or activities of the target company with those of the Group;
- incompatibility between marketing and employee management techniques;
- maintaining staff motivation and retaining key employees;



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- integrating the cultures of both companies;
- maintaining important strategic customer relationships;
- consolidating corporate and administrative infrastructures and eliminating duplications; and
- coordinating and integrating geographically separate organizations.

Moreover, even if the integration of an acquisition's operations is successful, the Group may not receive all the anticipated benefits, including in terms of the synergies, cost savings and growth opportunities expected. These benefits might not be obtained within the planned deadlines, or even never be obtained, which would have a material adverse effect on the Company's business, financial position, results of operations and prospects.

Furthermore, as a result of acquisitions, the Group may find itself forced to:

- use a substantial portion of its cash resources;
- increase its expenses and its debt level if the Group has to make additional borrowings to finance an acquisition;
- take on liabilities for which the Group is not indemnified by the former owners, given that indemnification obligations may also be the subject of litigation or concerns in connection with the solvency of the previous owners;
- lose existing or potential contracts owing to conflicts of interests;
- suffer adverse tax consequences or deferred compensation charges;

### **3.6 Risks relating to legal and administrative proceedings**

Teva Pharmaceutical Industries Ltd filed a notice of opposition on November 23, 2016 with the European Patent Office (EPO) against the European patent covering latanoprostene bunod and requested the revocation of the patent as a whole, alleging the absence of novelty or an inventive step. The European patent office rejected this notice of opposition and decided to maintain the patent as delivered. Teva Pharmaceuticals appealed this decision of the EPO on September 12, 2018.

At the end of August 2020, in its preliminary opinion, the Board of appeal of the European patent office concluded in the existence of an inventive step in the patent and invited the parties to file their observations by the end of December 2020. The date of the hearing has not been fixed to date.

The Group considers that the risk of invalidity of the patent is low, and in consequence has not recorded a provision for this contingency. However, this procedure is by nature uncertain and an unfavorable decision for the Company by this body would have a material adverse effects on its business and financial position (see section 18.7 "Judicial or arbitration proceedings" of this universal registration document.





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The Company contests the application of social security contributions on attendance fees paid to two non-employee directors whose tax residence is in the United States. By judgment of January 24, 2020, the Court of Justice of Nice granted the requests of the Company. This judgement has been appealed but, in the absence of diligence of the French social security body (URSSAF), the case has been struck off the role.

### **3.7 Insurance and risk coverage**

#### **3.7.1 Insurance**

##### *Civil liability of senior officers*

The Company purchased a global directors and officers liability policy for Group's senior officers (including directors) including coverage for defense costs before the civil and criminal courts, with a coverage limit for 2020 of €20,000,000 per period of insurance.

##### *General civil liability: Operational, product and professional civil liability*

The Company purchased a master policy to cover the civil liability of Nicox Group companies' operations, with a coverage limit for 2020 of €15,000,000 per claim for damage to third parties arising from their operations. The Company obtained an extension of guarantee for Product and Professional Liability in the amount of €15,000,000 per claim and per year of insurance with a deductible of €30,000 per claim. Lower limits of coverage exist for the different guarantees.

This Master Policy provides DIC/DIL (difference in conditions/difference in limits) coverage on top of a local civil liability policy obtained by Nicox Ophthalmics Inc. for the civil liability of the latter within a limit of USD 1,000,000 per claim and per insurance year.

Nicox Ophthalmics Inc. took out a compulsory insurance policy to reimburse the wages and medical expenses of employees involved in occupational accidents and diseases (Workers' Compensation) within a limit of USD 500,000 and USD 100,000 per claim.

Nicox Research Institute purchased coverage for civil liability, civil and criminal legal protection, property damage, products, premises, occupational accidents, death and disability for certain designated persons.

Premium for 2020 for the above insurance policies amounted to €220,452.

#### **3.7.2 Risk coverage**

Besides the insurance policies described in the preceding paragraph, the Company took precautions to ensure continued operations and to avoid any significant loss in the event of a major incident. The Company's computer data are stored on central servers located in a secure room as well as in a Tier 3 Datacenter. Daily backup over a rolling 5 day period, weekly and monthly backups are performed. A



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copy of the weekly backups is transferred to another Tier 3 Datacenter located more than 150 km from the first Datacenter. The Company entrusts the storage and backup of all materials relating to its clinical trials, its financial data and its human resources data to a specialist company.

### **3.8 Internal control system**

The Company has based the development, implementation and description of its internal control and risk management system on the framework published by the AMF (*Autorité des Marchés Financiers*) in 2010 for small and midcap companies.

It should be noted that the procedures described in this report apply to the parent company and all companies included in the Group's consolidated accounts. This report describes the situation as of December 31, 2020.

#### **3.8.1 Group objectives for Internal Audit:**

#### **3.8.2 The Group is implementing the structuring of its Internal audit mechanism over time**

In this respect, the Group notes that Internal Audit is a mechanism of the Company defined and implemented under its responsibility, and intended to ensure:

- Application of the instructions and strategies defined by Management;
- The reliability of financial information;
- Compliance with laws and regulations;
- The correct operation of the Group's internal processes, particularly those which help to protect its assets;

and, in general, it contributes to the control of its activities, the effectiveness of its operations and the efficient use of its resources. However, Internal Audit cannot provide an absolute guarantee that the Company's objectives will be met.

#### **3.8.3 Organization of Internal Audit**

The Nicox Internal Audit is based on organizational structures and methods responsible for direction and control, but also responsible for risk management.

The Board of Directors and its different committees:

#### ***The Board of Directors***

The Board of Directors is the leading player in the Group's Internal Audit. It has adopted internal rules that define, among other items, the responsibilities and procedures for the operation of the Audit Committee, the Compensation Committee, and the Corporate Governance Committee.





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#### ***The Audit Committee***

For the work of its Audit Committee, the Group relies on the report of the AMF working group on the Audit Committee (AMF Recommendation of July 22, 2010).

The Audit Committee, whose role is to advise the Board of Directors, is responsible for the following within the framework of the Internal Audit process:

- to monitor the effectiveness of the Internal Audit and risk management systems within the Group;
- to review the controls performed by the Finance Department to evaluate the relevance and effectiveness of the procedures in effect;
- to monitor the implementation of the recommendations developed on the basis of the results of the Finance Department's controls;
- to regularly review the Group's main financial risks and its significant off-balance sheet commitments;
- to take a position on any changes in accounting principles and the determinant financial statements judgments and estimates.

In the context of the missions it has been assigned, the Audit Committee may ask the Chair to provide it with any document or allow the committee to interview any person, particularly the Vice President for Finance and the Statutory Auditors, in order to obtain information about the specific accounting, financial and operational features of the company. The Audit Committee is regularly informed in reports of the progress on the different work being performed as part of the Internal Audit of Group companies.

#### ***The Compensation Committee***

The Compensation Committee, which has an advisory role with the Board of Directors, is responsible for the following within the Internal Audit process:

- to review annually the compensation, in-kind benefits, stock options and restricted stock units (*actions gratuites* or “free shares”) awarded to corporate officers and senior management employees, and the members of the Management Committee;
- to review the plan for long-term allocation of stock options and restricted stock units;
- to review the annual increase in employee payroll.

#### ***The Corporate Governance Committee***

The Corporate Governance Committee, which has an advisory role with the Board of Directors, is responsible for the following tasks within the Internal Audit process:

- to establish criteria to assess the independence of the members of the Board of Directors;

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- to evaluate and monitor corporate governance procedures;
- to verify the appropriate application of the regulations and recommendations on corporate governance;
- to examine candidates for corporate officers and senior management employees.

#### ***The Science and Technology Committee***

The Science and Technology Committee, which has an advisory role with the Board of Directors, is responsible for the following tasks within the Internal Audit process:

- Assisting the Board in supervising the scientific and technical aspects of the company's activities;

Examining the progress and performances of Management in achieving the objectives and limiting the associated risks;

#### ***The Management Committee***

In addition to the Board of Directors and its different committees, Internal Audit also relies on an operational committee: the Management Committee.

The Management Committee, led by the Chief Executive Officer is currently composed of four members. The Management Committee monitors the Group's plan, ensures respect for the operating plan and targets assigned by the Board of Directors at all management levels, and debates all organization and operational strategy questions placed on the agenda by its members.

In addition, it is responsible for defining, leading and monitoring the Internal Audit process best adapted to the Group's situation and activities. Within this framework, it is continually informed of any malfunctions, insufficiencies or difficulties in application. The Management Committee ensures the commitment to the correct actions necessary.

#### ***Advisory Committees***

The Group regularly organizes meetings of Advisory Committees composed of independent experts in order to exchange information on various issues related, in particular, to its business development activities and its new commercial activities. These committees provide an independent opinion and propose recommendations that assist the Group to make strategic and operational choices.

#### ***Quality Assurance and Finance Department***

Finally, the other players in Internal Audit are Quality Assurance and the Finance Department:

#### ***Quality Assurance (QA)***

The Quality management system is organized around two pillars:



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- Designing, preparing and managing a quality information system as reflected by procedures, instructions, forms and models. QA ensures the distribution of procedures and the homogeneity of formats and media used.
- Conducting quality audits to evaluate in an independent manner
  - Compliance with procedures and internal processes for the purpose of ensuring continuing improvement for operations;
  - The capabilities of suppliers and service providers for the purpose of guaranteeing compliance with applicable requirements.

#### ***The Finance Department***

The Vice President of Finance (with the support of QA for the document support area) is responsible for maintaining the Internal Audit process which is based on:

- continual update and improvement of the existing administrative and financial procedures;
- the establishment of new procedures, as needed;
- the availability of adapted information tools.

#### **3.8.4 Internal information distribution**

Disseminating information for making it possible to implement Internal Audit within the Group through Quality Assurance which directs production and centralizes all standard procedures through a Quality gateway after formal approval. Each newly issued procedure is transmitted in an accompanying email by Quality Assurance in order to:

- Summarize the objectives of the procedure;
- Indicate its application date.

A reply from each recipient is requested to ensure follow-up (confirmation that it has been read).

Each new employee receives an email from Quality Assurance which informs the employee where he can access the procedures for his department.

In addition, certain procedures are covered by internal training sessions in order to explain the content and responsibilities.

#### **3.8.5 Risk management**

In its management of risks, the Group relies on three main tools, which complete the Internal Audit process. This approach is moving it toward conformity with the transposition of the fourth and seventh European Directives, primarily by establishing a specific risk management process.

#### ***The universal registration document***



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Nicox prepares each year a universal registration document (URD) that includes a chapter on the risk factors that could have a material negative impact on its activity, financial position and results. This document deals with operational risk factors as well as financial, environmental, commercial and technological risk factors.

Faced with a number of these risks, the Group adopts a policy of precautions for risk insurance and coverage. Nicox believes that, as of this date, its insurance coverage is adequate for all the operations of its Group.

***Assessment of risk management***

There was no formal review of risk management in 2020

***Statutory Auditors' review of Internal Audit procedures***

The Statutory Auditors conduct a yearly review of the Internal Audit Procedures. The conclusions of this work are presented to the Finance Department and allow the Internal Audit teams to enhance the risk identification process. The answers provided by management are reconciled with the correct action plan.

In December 2020, the Auditors' work consisted of individual interviews with managers of the Company and walk-through tests on the functional processes of certain Company operations.

**3.8.6 Control activities**

**3.8.6.1 Internal control procedures relating to the preparation and processing of financial and accounting information**

**3.8.6.1.1. Accounting and financial management and organization**

***Parties involved***

The Group's company accounts are kept under the direction of the Vice President for Finance. The accounts of Nicox S.A., Nicox Research Institute Srl are maintained internally. The accounts of subsidiaries Nicox Ophthalmics Inc. and Nicox Science Ireland Limited (the company was dissolved effective August 2, 2020) were entrusted to an external service provider, as was the consolidation of the Group's financial results.

As part of their procedures on behalf of the parent company and the publication of its consolidated financial statements, the statutory auditors conducted an audit of companies included in the consolidation scope of Nicox S.A. and considered at December 31, 2020 as significant entities based on the thresholds set by them.

In addition, at December 31, 2020, the payroll function was outsourced.

***Forward-looking management tools***



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The Business Plan: This is a projected business model prepared for all Group operations over a time horizon of five years (or ten, if necessary). This document is prepared and updated regularly on the basis of the Group's strategic decisions, taking into account the different objectives to be achieved for each operational development, and also taking into consideration changes in the pharmaceutical markets, regulations and the competitive environment. Each update of the Business Plan is presented to the Board of Directors.

The “Annual Budget”: Every year in the final quarter of the year, the Group Finance Department prepares an annual Budget, in close collaboration with the operational departments. On the basis of the strategic objectives defined in the Business Plan, the Management Committee defines the Group's objectives for the coming year. These objectives are then approved by the Board of Directors and distributed to the operational departments. The various operational departments assess their detailed needs in terms of operating expenses, investments and equipment, and human resources. This information is centralized by the Vice President of Finance and the Group Management Controller. The Management Committee evaluates the various budget proposals and makes certain decisions. The finalized Budget is presented to the Audit Committee and then to the Board of Directors for approval. Achievements are monitored and analyzed every quarter as part of the annual reporting process and subject to a detailed review by the Audit Committee at the end of each quarter.

The Revised Budget: budget revision process carried out midyear. This process updates budget assumptions for the following six-month period by comparison of the actual figures for the year to date with the initial budget projection. The Revised Budget is presented to the Audit Committee and then to the Board of Directors.

The Business Plan: the Annual Budget and the Revised Budget compose a set of financial documents and statements intended for the operational departments, the Management Committee, the Audit Committee and the Board of Directors of the Group. These financial documents and statements are shared by a defined and limited group of users, for strictly internal use, and are not, under any circumstance or in any form, communicated to the public.

#### **3.8.6.1.2. Preparation of financial and accounting information**

##### ***The consolidated internal reporting system***

The internal reporting system is based on the collection and compilation of local general accounting and budget data/revised budget of all Group entities. The data are returned in the form of detailed reports and consolidated statements that reflect the discrepancies between actual and forecast data. Consolidation adjustments are recognized at the close of each half-year.

*Based on this information, the Finance Department produces each month, as part of a closing procedure, a monthly operating reporting document. This consists of various cost accounting financial statements, both for the reference month and year to date as well as an analysis of the most significant variances in relation to Budget and the Revised Budget excluding consolidation adjustments.*



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The operational reporting information is made available to line management departments. This report is presented every quarter to the Audit Committee.

Added to these monthly operational reporting items are an interim and annual consolidated report including in particular consolidation adjustments and a reconciliation table with the operational reporting information. This report is submitted to and discussed by the Audit Committee, and then submitted to the Board of Directors.

The consolidated monthly, semi-annual and annual reports are a major component of the financial information control system. They are favored by the Executive Committee as a monitoring, control and management tool. The reconciliation of accounting and forecast data, combined with the monthly analysis, ensures that the information produced is of high quality and reliable.

These reporting elements and analytical reviews are strictly for internal use and accessible to a defined and limited group of users. They are in no way and in no manner disclosed to the public.

***The consolidated financial statements***

The consolidated reporting system described above, and in particular the monthly report produced as part of a monthly closing procedure, is the basis on which the consolidated financial statements are prepared.

The procedures for escalating information from the subsidiaries to the parent company, along with the closing procedures, enable the parent company to prepare the consolidated financial statements. A closure timetable is circulated in the month preceding each closing to allow the various accounting divisions to arrange for all the necessary information to be submitted on time.

The consolidated accounts are closed semi-annually on June 30 and December 31 of each year (statutory accounting year-end date). They are subject to an audit by the statutory auditors on December 31 and to a limited review on June 30. The statutory auditors carry out a review of internal control procedures in the last quarter of each year.

The separate statutory financial statements of each Group company are prepared only as of December 31 of each year. Each subsidiary prepares its own financial statements (except in special cases as indicated above in the paragraph entitled Parties involved) according to the accounting standards applicable locally. For consolidation purposes, the data are restated using the Group's accounting standards (IFRS since January 1, 2005).

**3.8.6.1.3. Update of standard procedures relating to the preparation and processing of financial and accounting information**

The accounting manual and four (4) procedures dealing with the preparation and processing of accounting and financial information have remained in application since 2018.



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Procurement and contract management procedures were updated in 2020.**3.8.5.2 Information systems**

**3.8.7 Information systems**

During 2020, the reporting documents, business plan and budget were prepared using Excel.

**3.8.8 Oversight of the Internal Control system**

**3.8.8.1 Verification or Periodic Control of the proper implementation of procedures**

*Operational area*

Periodic control of operational areas was undertaken by Quality Assurance and is detailed in Section 3.8.6.3.2, which focuses on Quality Assurance work in 2020.

*Accounting and financial area*

The Group did not update the self-assessment record in 2020, including:

- The application guide for internal control of accounting and financial information;
- General internal control principles with regard to accounting and financial information;
- Questionnaires on internal control of accounting and financial reporting and on risk analysis and management.

**3.8.8.2 Reporting of work on Risks and Internal Control operations**

The work conducted on Risks and Internal Control operations is submitted by the Finance Department to the Audit Committee and is a major component of the risk management process.

This work involves the following:

Work in relation to the AMF Reference Framework (Selection of control points involving a self-assessment, identification of the scope of existence tests, proposed corrective action plan, selection of working processes for risk mapping);

- Improvement of the Internal Control system to encompass the updating of procedures, improved management tools, improved security and confidentiality of computer data, the conduct of audits by Quality Assurance.

**3.8.8.3 Work carried out in 2020 on Internal Control and Quality System management**

In 2020, the Company updated certain procedures as described in Section 3.8.5.1.2

**3.8.8.3.1 Monitoring work undertaken by Quality Assurance**



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The Quality Group was consolidated within the, Quality and Compliance functional entity. The Quality function covers all Group operations (research and development, the manufacture and surveillance of drugs).

At December 31, 2020, the process of simplifying and harmonizing quality documents is continuing with the goal of implementing identical Quality processes across all sites and subsidiaries (Nicox S.A, Nicox Research Institute S.r.l, Nicox Ophthalmics Inc.).

**3.8.83.2. Work undertaken in the field of IT**

The work in the IT area in 2020 was limited to maintenance and infrastructure rationalization. Given its size, the Group subcontracts IT services with an objective of ensuring the continuity of service.

**3.8.8.4 Areas for improvement in the Internal Control system**

**3.8.8.4.1. Adaptation of accounting and financial tools to the Group's new environment**

In 2020, the Company acquired a tool for invoices in electronic form that included an electronic approval process.

**3.8.8.4.2. Network architecture and IT security**

In 2020, the Group continued to adapt and rationalize the IT infrastructure of Nicox Group: by replacing obsolete equipment to ensure availability, the integrity and confidentiality of Nicox's IT infrastructure; by outsourcing as much as possible IT operations to guarantee continuity of service in the context of a small structure and by educating end users about information systems to assist them in becoming more autonomous with IT procedures and quality documents.

**3.8.8.4.3. Audit program conducted by the Quality Assurance**

Service providers (logistics, distribution, non-clinical development, pharmaceutical development, clinical development, the production of active ingredients and finished products, secondary packaging) were audited either for vendor approval purposes or oversight.

Three (3) External Audits were performed in 2020 concerning activities outsourced in 2020 by Group subsidiaries.



#### **4. INFORMATION ABOUT THE COMPANY**

##### **4.1 Company name and trade name of the Company**

The legal name of the Company is Nicox SA.

##### **4.2 Place of registration, registration number and legal identity number (LEI) of the Company**

Nicox SA is registered at the ‘registre du commerce et des societies’ (Company Register) of Grasse, France, (Postal code 06133) under the number 403 942 642. The Nicox SA APE code is 7211Z.

LEI code: 969500EZGEO9W4JXR353

##### **4.3 Date of incorporation and the length of life of the Company**

The Company was established on February 15, 1996 and registered on February 27, 1996 for a period expiring on December 12, 2094.

##### **4.4 Registered office and legal form of the Company legislation under which it operates, its country of incorporation, , the address and telephone number of its registered office and website**

Nicox SA is a French corporation with a Board of directors subject to the provisions of the Commercial Code. Its corporate headquarters are located at DRAKKAR D 2405 route des Dolines 06560 Valbonne Sophia Antipolis, France. Telephone number: +33 (0)4 97 24 53.00.

Website: [www.nicox.com](http://www.nicox.com). Information provided on the Company’s website does not constitute part of the original French language version of the universal registration document (*document d'enregistrement universel*) that was filed with the French Financial Market Authority, the AMF, with the exception of information expressly incorporated by reference into said document, and on that basis has not been reviewed or approved by the AMF.



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**5 BUSINESS**

**5.1 Overview**

**5.1.1 Summary of the main activities of the Company**

We are an international ophthalmology company developing innovative solutions to help maintain vision and improve ocular health. Nicox has two programs in late stage clinical development -- one in glaucoma (two Phase 3 trials) and one in blepharitis (one Phase 2b trial) -- a pre-clinical development candidate, and two licensed and commercialized products with exclusive partners.

- NCX 470, a novel nitric oxide (NO) donating prostaglandin analog, is currently in two Phase 3 clinical trials, Mont Blanc and Denali, for the lowering of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Top-line results from the Mont Blanc trial are currently expected in H1 2022 and those from the Denali trial in Q4 2022.
- NCX 4251, an innovative and patented suspension of nanocrystals of fluticasone propionate, is currently in Phase 2b clinical trial, Mississippi, for the treatment of acute exacerbations of blepharitis. Top-line results are currently expected in Q4 2021.
- NCX 1728, a development candidate selected from a new class of NO-mediated IOP lowering agents, for glaucoma.
- VYZULTA®, indicated for the reduction of IOP in patients with open angle glaucoma or ocular hypertension., is exclusively licensed worldwide to Bausch + Lomb, a Bausch Health Companies Inc. company, and commercialized in the U.S., Canada, Argentina and Mexico. VYZULTA has been also approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine.
- ZERVIAE®, indicated for the treatment of ocular itching associated with allergic conjunctivitis, is commercialized in the U.S. by our exclusive U.S. licensee Eyevance Pharmaceuticals or Eyevance, which was acquired by Santen Pharmaceutical Co., Ltd in September 2020. A Phase 3 clinical trial is currently being conducted in China by Ocumension Therapeutics, our exclusive Chinese partner for the development and commercialization of ZERVIAE in China. ZERVIAE is also exclusively licensed for development and commercialization in other territories.

Our lead product candidate, NCX 470, uses the same technology as VYZULTA, our commercialized product, by leveraging our proprietary expertise in generating novel patentable molecules, which we believe are new chemical entities (NCEs), that release NO. NO is a small signaling molecule that targets an intracellular enzyme, soluble guanylate cyclase (sGC). NO, naturally present in ocular tissues, plays a key role in the regulation of intraocular pressure, or IOP and can be linked with a pharmaceutical agent to potentially increase its effect on IOP lowering. Release of NO and the subsequent activation of sGC is one of the mechanisms that we believe leads to IOP lowering by Nicox's novel molecules. Adding NO to well-known molecules, such as prostaglandin analogs (PGAs), which is the most commonly prescribed class of IOP-lowering drugs, adds a potential second mechanism of action (MOA), and we believe allows certain of our products and product candidates to lower IOP further than the parent molecule alone. We believe that by designing our proprietary molecules with a dual MOA, we may be able to achieve greater IOP lowering compared to the parent compound alone.

*Product candidates*

NCX 470, discovered based on our proprietary NO-donating research platform, is our lead product candidate. NCX 470, which we believe is a NCE, is a novel NO-donating prostaglandin formulated as an ophthalmic solution, which is currently in late-stage clinical development for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Following a positive End-of-Phase 2 meeting with the U.S. FDA, the Company initiated the first Phase 3 clinical trial, Mont Blanc, in the U.S. on June 1<sup>st</sup>, 2020, evaluating NCX 470 for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The Mont Blanc trial is a multi-regional, double-masked, 3-month, parallel group trial evaluating the efficacy and safety of NCX 470



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ophthalmic solution, 0.1% compared to latanoprost ophthalmic solution, 0.005% in patients with open-angle glaucoma or ocular hypertension. The 0.1% dose was selected through an initial adaptive design portion of the trial. The primary efficacy evaluation is based on time-matched IOP at 8 AM and 4 PM at Week 2, Week 6 and Month 3. The trial is expected to randomize approximately 670 patients at approximately 50 clinical sites, primarily in the U.S. and a small number of clinical sites in China. Top-line results from Mont Blanc trial are currently expected in H1 2022. On November 9<sup>th</sup>, 2020 Nicox initiated the second Phase 3 trial in the U.S., Denali, financed jointly and in equal parts by Nicox and Ocumension. Denali is a 3-month Phase 3 trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1% versus latanoprost ophthalmic solution, 0.005%, for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The Denali trial, which will also include a long-term safety extension, is expected to randomize 670 patients, at approximately 50 clinical sites in the U.S. and China, with a majority of patients to be recruited in the U.S. The Denali trial, together with the Mont Blanc trial, are designed to fulfill the regulatory requirements for Phase 3 safety and efficacy Phase trials to support NDA submissions in the U.S. and China. Top-line results from the Denali trial are currently expected in Q4 2022. In the U.S., multicenter, dose-response, Phase 2 clinical trial, Dolomites, NCX 470 ophthalmic solution 0.065% demonstrated non-inferiority and statistical superiority, based on the trial's pre-specified statistical analysis plan of diurnal mean IOP reduction at Day 28, to latanoprost ophthalmic solution, 0.005%, the U.S. market leader in prostaglandin analog prescriptions. The molecules in VYZULTA and NCX 470, discovered using this technology, are believed to lower IOP through a dual MOA, which combines NO donation, that activates sGC, with PGAs that activate Prostaglandin F, or FP, receptors, to increase the compounds' ability to lower IOP relative to the parent active compounds. In NCX 470, our NO-donating research platform was applied to add an NO-donating group to bimatoprost. Bimatoprost (known by the brand name LUMIGAN) is a PGA and is the current market leader by sales value among all glaucoma therapies in the U.S. and EU, the two largest glaucoma markets worldwide. NCX 470's potential dual MOA is believed to lower IOP by increasing the outflow of fluid from the eye through the primary, or conventional outflow route via trabecular meshwork as well as through secondary, or unconventional outflow route via uveoscleral pathway. The primary outflow is believed to be increased by NO released from NCX 470 via activation of sGC and relaxation of trabecular meshwork while the secondary outflow pathway is believed to be increased by bimatoprost released from NCX 470 activation of FP receptors.

We are focusing our research efforts on ocular disorders in which NO is believed to play a major role in controlling IOP. Our research platform produced the NO-donating compounds, VYZULTA and NCX 470. VYZULTA demonstrated greater IOP lowering than the parent PGA compound in randomized clinical trials. This effect is believed to be due to the additional lowering in IOP from the NO-donating MOA. We are applying key learnings, based on Nicox's stand-alone NO-donors, to NO-donating moieties attached to other non-PGA therapeutic classes of compounds with the goal of enhancing the NO-mediated effects. NCX 1728 is the first in a new class of compounds in which NO-mediated effects are enhanced by concomitant phosphodiesterase-5 (PDE5) inhibition activity within the same molecule. PDE5 inhibition has been shown both to enhance the efficacy and the duration of NO-mediated effects. This class has the potential for development alone, as adjunctive therapy or in fixed-dose combinations with latanoprost or other PGAs for lowering IOP in patients with glaucoma or ocular hypertension.

In addition to our NO-donating product candidates in pre-clinical and clinical development, our pipeline includes a product candidate based on a novel and proprietary formulation of well-established molecule that has previously been used in other indications and therapeutic areas, with the potential to offer novel treatments for various eye conditions.

NCX 4251, our novel patented ophthalmic suspension of fluticasone propionate nanocrystals, is being developed as a targeted topical treatment of the eyelids for patients with acute exacerbations of blepharitis, a common eye condition characterized by eyelid inflammation. Fluticasone propionate, the active ingredient in NCX 4251, is a well-established corticosteroid which has been marketed for more than 20 years for a number of non-ophthalmic indications, including asthma and allergic rhinitis, and it has an affinity for the glucocorticoid receptor approximately ten times greater than dexamethasone, a corticosteroid commonly used in ophthalmology. We believe that this is the first time that fluticasone propionate is being developed for an ophthalmic indication, and that NCX 4251 is the first product candidate developed as a targeted topical treatment of the eyelids for patients with acute exacerbations of blepharitis. Mississippi, a Phase 2b clinical trial of NCX 4251, evaluating once-daily dosed NCX 4251 0.1% versus placebo in patients with acute exacerbations of blepharitis was initiated in the U.S. on December 14<sup>th</sup>, 2020. The Mississippi trial is expected to randomize 200 patients at 5 to 10 clinical sites across



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the U.S. The primary outcome measure is the proportion of patients achieving complete cure in eyelid redness, eyelid debris and eyelid discomfort, the hallmark signs and symptoms of blepharitis, at Day 15. Secondary outcome measures also include signs and symptoms of dry eye disease. Top-line results of the Mississippi trial are currently expected in Q4 2021. Should NCX 4251 meet the primary efficacy endpoint for blepharitis, the Mississippi trial could represent the first of two pivotal trials needed to support an NDA submission for the treatment of blepharitis in the U.S. Nicox completed the U.S. multicenter, dose escalating, first-in-human, 36-patient Danube Phase 2 clinical trial with NCX 4251 which evaluated its safety and tolerability in patients with acute exacerbations of blepharitis. In the Danube trial, NCX 4251 met the primary objective of selecting the dose for further development. The NCX 4251 0.1% once daily (QD) treatment was selected to advance into a larger Phase 2b clinical trial. In that trial, the selected dose of NCX 4251, 0.1%, also demonstrated promising efficacy against exploratory endpoints in reducing signs and symptoms of dry eye disease.

### *Products*

Our lead commercial product, VYZULTA (latanoprostene bunod ophthalmic solution), 0.024%, represents the first FDA-approved drug developed based on our proprietary NO-donating research platform. In VYZULTA, an NO-donating group was linked to latanoprost, the active ingredient in XALATAN, a PGA, structurally related to prostaglandins. PGAs are in a class of molecules used in ophthalmology to lower IOP and are believed to do so by activating FP receptors located on the surface of cells. In the U.S., PGAs are the first line and the most commonly prescribed pharmacotherapy class for the lowering of IOP in glaucoma and ocular hypertensive patients. VYZULTA is the first PGA approved by the FDA for the reduction of IOP with one of its metabolites being NO. NO is believed to lower IOP by increasing the outflow of fluid from the eye via activation of sGC, a different mechanism from that of PGAs. Thus, VYZULTA is believed to possess a dual MOA in a single molecule. Prior to the FDA approval of VYZULTA, there were no other NO-donating products approved for the lowering of IOP in the U.S. VYZULTA is exclusively worldwide licensed to Bausch + Lomb, a Bausch Health Companies Inc. company, and is commercialized in the U.S., Canada, Argentina and Mexico. VYZULTA has been also approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine.

ZERVIAE (cetirizine ophthalmic solution), 0.24%, our second FDA-approved product, is a novel formulation of cetirizine developed and approved for the first time for topical application in the eye. ZERVIAE, which is indicated for the treatment of ocular itching associated with allergic conjunctivitis, is the first product for the topical treatment of ocular allergies to use cetirizine, the active ingredient in ZYRTEC, a well-established oral antihistamine which has been marketed for over 20 years. We believe that the proven safety and efficacy of oral cetirizine currently recognized by physicians will encourage the adoption of ZERVIAE ophthalmic solution. In 2017, we granted Eyeavance exclusive rights to commercialize ZERVIAE in the U.S. and transferred the New Drug Application, or NDA, to Eyeavance. ZERVIAE has been commercialized in the U.S. by Eyeavance since March 2020. ZERVIAE has also been exclusively licensed for development and commercialization to Ocumension in the Chinese and majority of South East Asian Region markets, to Samil in South Korea, and to ITROM in Gulf and Arab markets. Ocumension initiated a Phase 3 clinical trial in China with ZERVIAE in December 2020. Subject to any additional data requested by the Chinese NMPA, this Phase 3 trial, in addition to the data package used by the FDA for ZERVIAE in the United States, is expected to be sufficient to support a Chinese NDA.

### *Ophthalmic Products Market*

The current treatment landscape for open-angle glaucoma is dominated by two drug classes, topical PGAs and topical beta-blockers, with various combinations introduced over the past 20 years. Since PGAs began to replace topical beta-blockers as first line IOP-lowering agents in glaucoma, several have been approved and generic competition in the category is significant. In the U.S., PGAs have replaced beta-blockers as the first line therapy. Prior to the approval of VYZULTA, there had been no IOP-lowering drugs with new MOAs approved in U.S. and European Union since the launch of the first PGA more than twenty years ago. This is a situation which we believe has resulted in a significant demand from eyecare providers for new MOAs to lower IOP in patients with glaucoma.

Allergic conjunctivitis is currently treated by both oral and topical ocular antihistamines, with more serious cases requiring topical or even oral corticosteroids. The treatment regimens and molecules are well established and most oral antihistamines are now available as generics in the U.S., frequently without prescription,



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along with some topical antihistamines. Nevertheless, new products in the field are necessary to expand the choices available to doctors and patients.

The blepharitis market is not well-defined. While there are antimicrobial and antibiotic ointments and eye drops indicated for the treatment of blepharitis, among other conditions, we believe that there are no products solely and specifically indicated for the treatment of acute exacerbations of blepharitis. We believe that this creates a significant opportunity for future therapies specifically developed for blepharitis. Topical steroids, antibiotics and their combinations are often prescribed to treat acute and chronic blepharitis. In addition to the pharmacotherapy, current standards of care include swabbing the eyelids with diluted non-irritative shampoo solution.

Worldwide, the sales of pharmaceutical ophthalmic treatments reached \$21.9 billion in 2019 and have grown at an average rate of 6% annually since 2015, according to IQVIA Health Analytics. In the U.S. alone, ophthalmology sales reached \$8.8 billion in 2019, growing also at an average rate of 6% annually since 2015. With respect to our markets of focus, worldwide sales of treatments targeting glaucoma were \$6.6 billion, representing 30% of the \$21.9 billion worldwide market for ophthalmic drugs and sales. In the U.S. treatments targeting glaucoma generated approximately \$3.2 billion in the U.S. in 2019, growing at an average annual rate of 6% since 2015 and representing 37% of the \$8.8 billion total ophthalmic drug sales in the U.S. for 2019. While there are no approved treatments solely indicated for blepharitis, we estimate that the market potential for the treatment of acute exacerbations of blepharitis in the U.S. alone could be more than \$700 million annually, and expect it to reach over \$1 billion by 2024. Additionally, prescription topical treatments for ocular allergies generate approximately \$400 million annually in the U.S., not including substantial sales of non-prescription and over-the-counter products used to alleviate symptoms of ocular allergies.

Our intellectual property portfolio consists of patents and pending patent applications related to composition of matter, pharmaceutical compositions and methods of use for our product candidates. We have patent protection in the U.S. for VYZULTA (through 2025), ZERVIAE (through 2032) and our product candidates NCX 470 (composition of matter protection in the U.S. until 2029 and formulation patent until 2039), and NCX 4251 (through 2033). These dates do not include potential patent extensions which may be available to us. Specifically, we expect the U.S. patent for VYZULTA to be extended to 2030.

As of December 30, 2020, we had 34 employees, including personnel supporting our development operations in the U.S. and France, and research and nonclinical development operations in Italy. Our headquarters is located in Sophia-Antipolis, Valbonne, France, and we have been listed on Euronext Paris (COX.PA) since 1999.

### **5.1.2 Our Competitive Strengths**

We believe the following key competitive strengths are core to our ability to develop novel treatment solutions for our patients and become a leader in ophthalmology:

- Our clinical-stage pipeline, consisting of novel therapies targeting inadequately met or unmet medical needs within ophthalmology, including glaucoma and blepharitis;
- Our proven NO-donating research platform, which we believe provides a competitive advantage for the discovery of innovative product candidates for the lowering of IOP, as validated by VYZULTA and further demonstrated by the results of the NCX 470 Dolomites Phase 2 clinical trial;
- Our products commercialized in the U.S., VYZULTA (which is also commercialized in certain other territories outside of the U.S.) and ZERVIAE, both of which may potentially be able to obtain marketing approval in other countries where the data submitted to FDA are sufficient, or new data can be generated, for such approval;
- Our ability to identify and effectively advance additional product candidates, such as NCX 1728, both through our internal research and development efforts and through possible in-licensing





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opportunities or acquisitions of additional ophthalmic products or product candidates that would complement our current product portfolio;

- Our proven ability to enter into successful partnerships with leading biopharmaceutical companies, as demonstrated by our worldwide exclusive licensing agreement with Bausch + Lomb for VYZULTA, to enter into regional collaboration agreements as demonstrated by the exclusive licensee agreements with Ocumension and to enter into commercialization partnerships, as demonstrated by our exclusive licensing agreement with Eyeavance and as well by the development and commercialization agreements with Ocumension, Samil and ITROM;
- Our significant experience in ophthalmic drug discovery and development as well as extensive operational, financial and public company experience across both our management team and our board of directors. Our key executives and board members have held leadership roles within major pharmaceutical ophthalmology companies, including divisions of Alcon, Inc., Allergan, Inc., Novartis AG, Inspire Pharmaceuticals, Inc., Parion Sciences, Inc. and ISTA Pharmaceuticals, Inc.

### 5.1.3 Our Strategy

Our goal is to become a fully integrated ophthalmology pharmaceutical company focused on the discovery, development and commercialization of novel therapeutics for eye diseases with inadequately met need or unmet medical needs.

Key elements of our strategy include:

- ***Rapidly advance our product candidates through clinical development to approvals in the U.S.*** Our pipeline includes NCX 470 for glaucoma and NCX 4251 for blepharitis. We plan to develop and commercialize our product candidates internally in key markets including the U.S. and to keep the rights for Europe for potential future partnerships or for direct marketing;
- ***Optimize development through partnerships.*** We are seeking to optimize development and commercialization of our product candidates outside of the U.S. through regional collaborations where we can leverage the resources of a partner, such as our partnerships with Ocumension on NCX 470 in the Chinese, Korea and South East Asian markets and NCX 4251 in the Chinese market. In certain instances, we may partner a program for exclusive development;
- ***Advance the development of our product candidates.*** Nicox plans to advance the development of NCX 1728, the first development candidate selected from a new class of NO-mediated IOP-lowering agents. The Company also evaluates in-licensing or acquisition opportunities for additional ophthalmic product candidates or products.
- ***Leverage the royalty revenues from VYZULTA in the field of glaucoma, in partnership with Bausch + Lomb.*** Under the terms of our worldwide exclusive license agreement, Bausch + Lomb is responsible for all commercialization activities. We are eligible to receive future net milestones and tiered net royalties from Bausch + Lomb of up to \$150 million and 6% to 12%, respectively, after deduction of payments due to Pfizer under the 2009 agreement whereby we regained the rights to VYZULTA. We believe Bausch + Lomb's experience in commercialization of ocular products will allow us to realize significant benefits from this partnership;
- ***Maximize the value of ZERVIAE through partnering.*** In September 2017, we entered into an exclusive licensing agreement with Eyeavance for the commercialization of ZERVIAE in the U.S. where it has been marketed since March 2020. We also entered into exclusive development and commercialization license agreements with Ocumension for the Chinese market in March 2019, expanding the rights to the majority of South East Asian markets in March 2020, with Samil in South Korea in December 2019 and also with ITROM in Gulf and Arab markets in August 2020. Similar to VYZULTA, we believe this strategy will allow us to efficiently use our internal resources while



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providing significant financial benefit. We are currently seeking partners capable of pursuing approval for and marketing ZERVIAE in other countries outside the U.S.

**5.1.4 Description of the Eye**

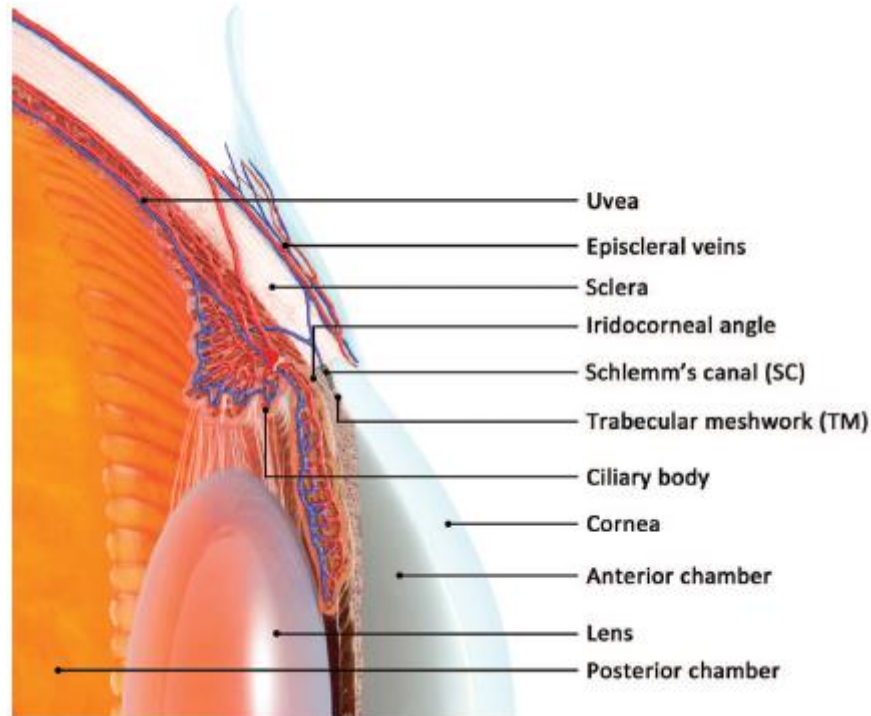
The eye is a fibrous globe that maintains its spherical geometry by being filled with a fluid called aqueous humor on the front side of the eye adjacent to cornea (also called the anterior segment) and a gel called vitreous humor on the back side of the eye adjacent to retina (also called the posterior segment). Both the front of the eye and the back of the eye are at the proper pressure to maintain the eye's shape and thus maintain an unobstructed and optically clear path for the light through the cornea and the lens to the retina. To maintain the pressure on the front of the eye, and therefore its shape, the aqueous humor is constantly produced inside the front compartment of the eye by a tissue known as the ciliary body and flows forward through the pupil and into the angle defined by the front of the iris and the back of the cornea. Blockages or malfunctions in this drainage system can result in abnormally high IOP often resulting in glaucoma.

Blepharitis is a condition in which the margins of the eyelids become painful, red and swollen and may contain dandruff-like matter, as shown in the picture below, and occurs in two forms. Anterior blepharitis affects the outside front of the eyelids, where the eyelashes are attached, and is most commonly caused by bacteria, demodex (a tiny mite that lives in hair follicles) and scalp dandruff. Posterior blepharitis affects the inner edge of the eyelids, the moist part which makes contact with the tear film of the eye, and is most commonly caused by problems with certain eyelid oil glands, or meibomian glands. Acne, rosacea and scalp dandruff can also cause posterior blepharitis. Both forms of blepharitis are associated with significant inflammation of the eyelid.

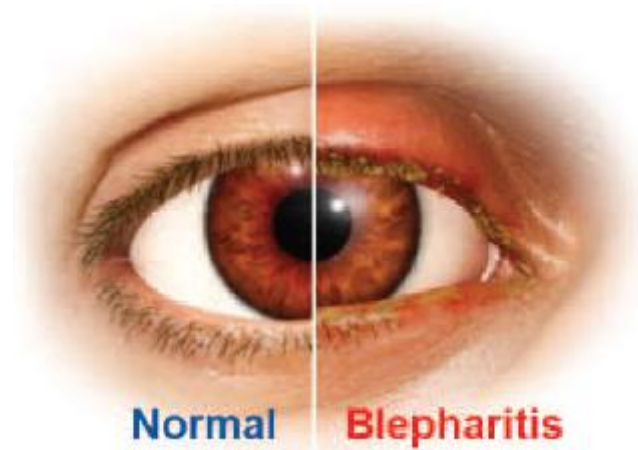


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The picture below shows the cross section of the aqueous humor drainage system of the eye.



The picture below shows the inflammation (redness and swelling) of the eyelid associated with blepharitis.















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**5.1.5 Our Pipeline**

We believe that our pipeline is strong in glaucoma and broadly across eye diseases of the anterior segment (i.e. the front of the eye), with two products commercialized, one product candidate in Phase 3 clinical development and another one in Phase 2b as well as one program in early-stage development. The future development of the Company depends on the outcome of the development activities of the Company and its ability to finance them.

The following table summarizes key information about our approved and commercialized products, and product candidates in preclinical and clinical development:

Products and product candidates/ Indications		Stages of Development						Expected milestones
		Preclinical	Phase 1	Phase 2	Phase 3	NDA	Marketed	
NO-Donating Product Candidates Targeting Glaucoma								
NCX 470 second generation NO-donating bimatoprost analog   Glaucoma	<div><div></div><div></div><div>Chinese market</div></div>							First Phase 3 top-line results H1 2022
NCX 1728 novel NO-mediated IOP lowering agent   Glaucoma	<div><div></div></div>							Entry into pre-IND development
Novel Formulation Targeting Blepharitis / Dry Eye Disease								
NCX 4251 fluticasone propionate Blepharitis   Dry eye disease	<div><div></div><div></div><div>Chinese market</div></div>							Phase 2b top-line results Q4 2021 Phase 2 start
Out-Licensed Commercial Products								
VYZULTA® Glaucoma	<div><div></div><div>Worldwide</div></div>							Revenue growth
ZERVIA™ Allergic conjunctivitis	<div><div></div><div>United States</div></div> <div><div></div><div>Chinese market</div></div>							Revenue growth Phase 3 results



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*Overview*

Our product candidate pipeline features clinical and early development stage assets with a potential to offer novel treatments in various eye conditions. Those targeting the lowering of IOP in patients with open-angle glaucoma or ocular hypertension are from our proprietary NO-donating research platform. We are also developing a novel and proprietary formulation of a well-established molecule that has previously been used in other indications and therapeutic areas.

In addition, we have two commercialized products; VYZULTA, commercialized in the U.S., Canada, Argentina and Mexico, and which is also approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine, by our exclusive worldwide licensee, Bausch + Lomb, and, ZERVIA, commercialized in the U.S. since March 2020 by our exclusive U.S. partner EyeVance.

*Using NO in ophthalmology*

We have developed a leading position in the therapeutic application of NO-donating molecules in ophthalmology. Our compounds are designed to release NO with a pharmacological benefit believed to be elicited locally at the tissue level via NO activation of the intracellular enzyme sGC expressed within ocular tissues. Consistent with our strategic positioning in ophthalmology, our research platform is focused on eye conditions where NO has been shown to play an important role.



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NO is a small signaling molecule whose target is an intracellular enzyme, sGC, which converts guanosine triphosphate to the second messenger, cyclic guanosine monophosphate, or cGMP. The cellular machinery, that synthesizes endogenous NO, is present in ocular tissues, together with other components involved in the NO-signaling cascade via the activation of sGC. The NO stimulated increase in the concentration of cGMP in the trabecular meshwork leads to the sequestration of intracellular calcium, relaxation of the trabecular meshwork and, consequently, an increase in the outflow of the aqueous humor from the anterior segment of the eye through the primary or conventional outflow pathway (i.e., via the trabecular meshwork, Schlemm's canal, aqueous veins, and episcleral veins). All of the foregoing events are thought to lead to lowering of IOP. The effect of NO in the sGC signaling cascade may be further increased or prolonged by sGC stimulators, which interact synergistically with NO to increase the production of cGMP. Additionally, the effect of NO on IOP lowering may be further increased and/or prolonged by PDE5 inhibitors, which inhibit the degradation of cyclic guanosine monophosphate (cGMP), a key intracellular messenger that is produced as a result of stimulation by NO. Studies have shown that topical administration of traditional NO donors, such as nitroglycerin or isosorbide mononitrate, reduces IOP, reinforcing the role of NO in IOP regulation. Lower plasma levels of NO markers are found in open angle glaucoma patients compared to individuals without glaucoma. Several studies conducted in animal models, as well as in glaucoma patients, have shown that the release of NO activates sGC and lowers IOP.

To date, it has been established that NO plays a key role in the regulation of IOP. An NO-donating moiety can be linked to other pharmaceutical agents to improve IOP-lowering efficacy, as is the case with our lead clinical development candidate NCX 470, a novel NO-donating prostaglandin analog, and our commercialized product with the same mechanism of action, VYZULTA. Release of NO and the subsequent activation of sGC is one of the mechanisms that is believed to lead to IOP-lowering by our novel molecules. We believe that by designing our proprietary molecules with a dual MOA, we may be able to achieve increased IOP lowering compared to the parent compound alone. Based on this approach, our partnered approved product VYZULTA and our product candidate NCX 470 currently in clinical development, are comprised of a parent PGA and a NO donor. NCX 470, a novel NO-donating prostaglandin analog, has demonstrated statistical superiority to latanoprost, based on pre-specified statistical analysis plan of IOP reduction, in the Dolomites Phase 2 trial. We believe that NCX 470 has the potential to become the first approved non-combination product with statistical superiority to a prostaglandin analog. We also believe that NCX 470 has the potential to lower IOP more than bimatoprost, an FDA-approved PGA that is the current U.S. market leader by sales marketed under the brand LUMIGAN. The results from the Dolomites Phase 2 trial on NCX 470 together with the positive clinical Phase 2 and 3 results obtained with latanoprostene bunod and the subsequent approval of VYZULTA by the FDA demonstrate the potential of such dual MOA approach with our proprietary NO-donating research platform in ophthalmology. Apart from VYZULTA, there are currently no NO-donating molecules approved for ophthalmic indications in the U.S.

### *NO-donating research platform and ongoing research activities*

We have developed a leading scientific and strategic position in the therapeutic application of NO-donating compounds based on our proprietary NO-donating research platform. Using this proprietary expertise in generating novel, patentable molecules, which we believe are NCEs, that release NO, our research center has conducted lead generation and lead evaluation in preclinical studies in ophthalmology, creating a significant patent portfolio.

We are focusing our research efforts on ocular disorders where NO is believed to play a major role in controlling IOP. Our research platform produced the NO-donating compounds, VYZULTA and NCX 470. VYZULTA has demonstrated greater IOP lowering than the parent PGA compound in randomized clinical trials. This effect is believed to be due to the additional lowering in IOP from the NO-donating moiety. We are applying key learnings, based on Nicox stand-alone NO-donors, to NO-donating moieties attached to other non-PGA therapeutic classes of compounds with the goal of enhancing the NO-mediated effects. NCX 1728 is the first in a new class of compounds where NO-mediated effects are enhanced by concomitant phosphodiesterase-5 (PDE5) inhibition activity within the same molecule. PDE5 inhibition has been shown both to enhance the efficacy and the duration of nitric oxide-mediated effects. This class has the potential for development alone, as adjunctive therapy or in fixed-dose combinations with latanoprost or other PGAs for lowering IOP in patients with glaucoma or ocular hypertension.



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*Mechanism of action of NO and NO-donating prostaglandin analogs*

Evidence suggests that PGAs, which are indicated for reducing elevated IOP in patients with open-angle glaucoma or ocular hypertension, have a MOA which works via prostaglandin FP receptor activation with a primarily positive impact on the activity of certain enzymes, resulting in a widening of the interstitial spaces of the ciliary muscle and contributing to increased uveoscleral outflow of the aqueous humor. This pathway is referred to as the nonconventional or the secondary pathway. However, the conventional or the primary pathway, wherein aqueous humor exits the eye through the trabecular meshwork into Schlemm's canal, a circumferential vessel in the angle of the eye between the cornea and the iris that collects the aqueous humor from the anterior chamber and delivers it to the venous blood vessels, is believed to be a major limiting factor in aqueous humor outflow, and the flow through the primary or conventional pathway is decreased in glaucoma. PGAs may have only a small impact on this pathway.

Because the primary or conventional pathway is known to be NO-sensitive, we sought to create a compound that would both release a prostaglandin analog to target the uveoscleral and secondary pathway by activating FP receptors and, at the same time, release NO to stimulate sGC to target the primary or conventional pathway in order to achieve a novel dual MOA. Through investigating this mechanism, latanoprostene bunod was discovered in our research center in Italy. Latanoprostene bunod (the active ingredient in VYZULTA) is an NO-donating version of an existing drug, latanoprost, which belongs to the category of prostaglandin F2-alpha analogs. Latanoprostene bunod is metabolized, after application on the ocular surface, into latanoprost acid and another moiety which is then further metabolized to release NO.

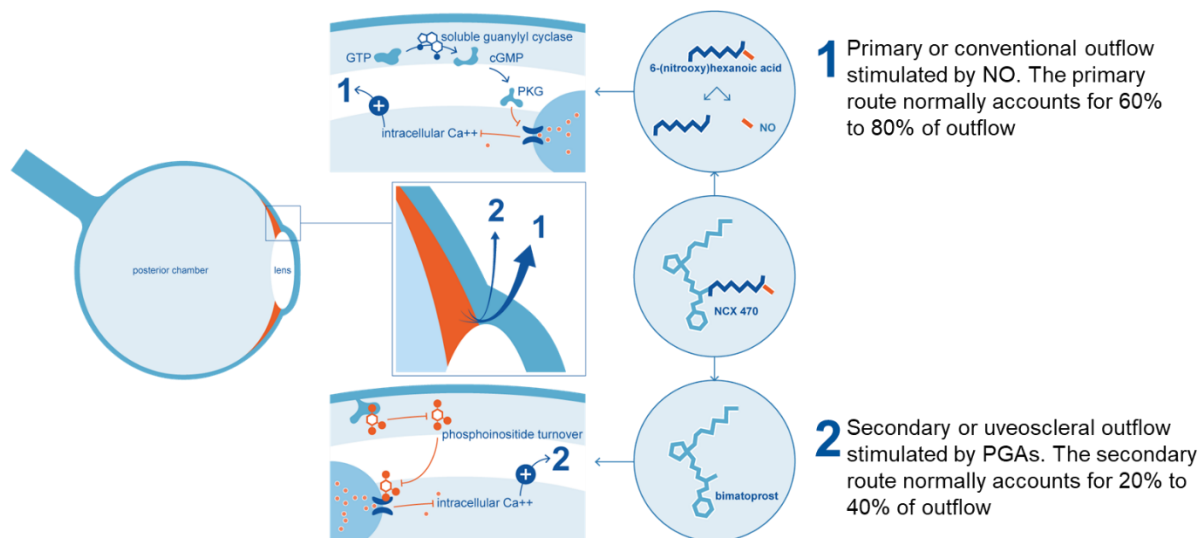
The preclinical and clinical data demonstrate that latanoprostene bunod lowers IOP to a greater extent than latanoprost alone in multiple animal models and in glaucoma patients. Our partner, Bausch + Lomb, conducted preclinical studies to investigate the effect of latanoprostene bunod on primary human trabecular meshwork cell contractility to determine whether latanoprostene bunod might mediate this additional IOP lowering through the conventional outflow pathway. Results from these preclinical studies support the concept that latanoprostene bunod has a dual MOA and may target both aqueous outflow pathways to lower IOP in patients with glaucoma or ocular hypertension. These data have been further supported by results of a Phase 2 clinical trial of latanoprostene bunod versus latanoprost conducted in glaucoma and ocular hypertension patients.

As mentioned above, NCX 470 is a novel NO-donating prostaglandin analog that we believe has the potential to become the first non-combination product with statistical superiority to a PGA (latanoprost) and to lower IOP more than bimatoprost, an FDA-approved PGA that is the current U.S. market leader by sales marketed under the brand LUMIGAN. Both NCX 470 and VYZULTA are designed to lower IOP via two MOAs. Upon administration to the eye, NCX 470 and VYZULTA are transformed by certain enzymes present in the eye into the prostaglandin analogs, bimatoprost acid and latanoprost acid, respectively, and the NO-donating moiety. This NO-donating moiety is then further transformed, breaking down into NO and inactive organic compounds. The prostaglandin analog, one active component of NCX 470 and VYZULTA, is released in the eye and is believed to interact with specific receptors (prostaglandin F2 alpha receptors). This interaction is thought to trigger signaling cascades that ultimately lead to rearrangement of the smooth ciliary muscle in the eye's middle layer, called the uvea, which in turn improves the outflow of the fluid present in the eye, or aqueous humor, from the fluid-filled chamber at the front of the eye backwards through the uvea and sclera (the white fibrous capsule of the eye). This outflow is referred to as the uveoscleral, unconventional or secondary outflow pathway. NO, the second active component released by NCX 470 and VYZULTA, is thought to enhance the outflow of the eye fluid by the conventional or primary outflow pathway, by modulating the eye tissues called the trabecular meshwork and changing the structure of a canal inside the eye known as Schlemm's canal. The released NO is thought to trigger signals leading to a decrease in cell contractility and volume and, thus, allowing an enhancement of the conventional outflow pathway.

The picture below shows the MOAs of NO-donating PGAs: The trabecular meshwork outflow, also known as the primary or conventional outflow pathway, which is NO sensitive and the uveoscleral outflow, the secondary or non-conventional outflow pathway that is prostaglandin sensitive.



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*Glaucoma Overview*

Glaucoma is a group of ocular diseases in which the optic nerve is injured, leading to irreversible, permanent peripheral and, ultimately, central visual field loss. Glaucoma can eventually progress to blindness if not treated and is currently considered to be the second leading cause of irreversible permanent blindness worldwide. Glaucoma is frequently linked to high IOP (generally approximately above 22 mmHg) due to blockage or malfunction of the eye's aqueous humor drainage system in the front of the eye. Current medications are targeted at lowering IOP to slow the progression of the disease. Numerous eye drops are available to either decrease the amount of fluid produced in the eye or improve its flow out of the eye. Nearly half of all patients with open-angle glaucoma require more than one medication to lower their IOP to a target level at which visual field loss is likely to be minimized or halted. The requirement for multiple medications to lower an individual patient's IOP to their target level highlights the need for more effective treatments.

High IOP usually does not cause any symptoms, except in cases of acute angle closure where the IOP may rise to three or four times that of normal IOP, but can lead to optic nerve damage and vision loss if left untreated. Optic nerve damage and vision loss can also occur in patients with normal IOP, normotensive glaucoma patients, who are also treated with IOP lowering medications. The Normal Tension Glaucoma Study completed in 1998 showed that lowering IOP slowed the progression of normal-tension glaucoma, a form of glaucoma in which the patient's IOP is within normal ranges.

IOP lowering is associated with a decreased risk in progression to open-angle glaucoma in subjects with ocular hypertension, as well as progression of visual field loss in patients with open-angle glaucoma; every mmHg of IOP-lowering results in a risk reduction in open-angle glaucoma progression of approximately 10% to 20%. Patients with open-angle glaucoma who attain target IOP-lowering have a lower risk of disease progression and vision loss.

In 2019, worldwide sales of treatments targeting glaucoma were \$6.6 billion representing 30% of the \$21.9 billion worldwide market for ophthalmic drugs. In the U.S., sales of treatments targeting glaucoma totaled \$3.2 billion in 2019 (approximately 36 million prescriptions) or 37% of the \$8.8 billion U.S. market for ophthalmic drugs. Of the U.S. sales of treatments targeting glaucoma, \$1.5 billion, or nearly 50%, were sales of prostaglandin analogs, of which almost 90% were branded products led by LUMIGAN and TRAVATAN Z. Over 70% of the prostaglandin analog prescriptions are for generic latanoprost. Prostaglandin analogs are currently used as the first line pharmacotherapy in the U.S. standard of care.

While not derived from head-to-head trials, the table below provides a summary of the U.S. FDA labeling information for the currently used first-line pharmacotherapies.



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*Summary of the U.S. FDA Labeling Information for the Currently Approved First-line Pharmacotherapies for the Treatment of Glaucoma Patients with Ocular Hypertension.*

	<b>XALATAN(1) (latanoprost 0.005%)</b>	<b>LUMIGAN(1) (bimatoprost 0.01%)</b>	<b>TRAVATAN Z(1) (travoprost 0.004%)</b>	<b>VYZULTA(2) (latanoprostene bunod 0.024%)</b>	<b>ROCKLATAN(1) (latanoprost 0.005% and netarsudil 0.02%)</b>
IOP reduction.....	6 to 8 mmHg	Up to 7.5 mmHg (7 to 8 mmHg for 0.03% bimatoprost)	7 to 8 mmHg	Up to 7 to 9 mmHg	6.8 to 9.2 mmHg 1 to 3 mmHg greater than latanoprost or netarsudil (1.58 mmHg greater than latanoprost 0.005% at 3 months)(3)
Patient mean baseline IOP .....	24 to 25 mmHg	23.5 mmHg (26 mmHg for 0.03% bimatoprost)	25 to 27 mmHg	26.7 mmHg	23.6 mmHg(4)
Adverse reactions	Foreign body sensation 13%; punctate keratitis 10%; stinging 9%; conjunctival hyperemia 8%	Conjunctival hyperemia 31% (45% for 0.03% bimatoprost)	Conjunctival hyperemia 30% to 50%	Conjunctival hyperemia 6%; eye irritation 4%; eye pain 3%; instillation site pain 2%	Conjunctival hyperemia 59%; instillation site pain 20%; corneal verticillata 15%; conjunctival hemorrhage 11%

(1) Indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

(2) Indicated for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

(3) See Section 14, Clinical Studies, Figure 1 and 2 of ROCKLATAN package insert for diurnal IOP at Day 90 for ROCKLATAN vs. Latanoprost including both Mercury-1 and Mercury-2 IOP values (1.5; 1.7; 1.3; 1.5;2.0; and 1.5 mmHg).

(4) See Section 14, Clinical Studies, Figure 1 and 2 of ROCKLATAN package insert for baseline IOP for ROCKLATAN including both Mercury-1 and Mercury-2 IOP values (24.8; 23.7; 22.6; 24.7; 23.3; 22.4 mmHg).

For patients whose glaucoma is not well-controlled on a single PGA eye drop, adjunctive therapies are added on the top of PGAs as second, third and fourth eye drops. The adjunctive therapies include beta blockers, alpha agonists, carbonic anhydrase inhibitors, rho kinase inhibitors, or their fixed dose combinations. The total sales of adjunctive therapies accounted for approximately \$1.7 billion of the \$3.2 billion U.S. sales of treatments targeting glaucoma in 2019. Currently, it is estimated that 3.5% of the worldwide population between 40 and 80 years of age are affected by the most common forms of glaucoma, and it is estimated that, in 2018, around 36 million prescriptions were written in the U.S. annually for glaucoma drugs.

## **Product Candidates in our Pipeline**

### ***NCX 470—Our Lead Product Candidate***

NCX 470, which we believe is an NCE, is formulated as an ophthalmic solution of this novel NO-donating PGA in development for the lowering of IOP in patients with open-angle glaucoma and ocular hypertension. NCX 470 has been evaluated in the Dolomites safety and efficacy Phase 2 clinical trial and is currently in two Phase 3 trials, Mont Blanc and Denali. NCX 470 is designed to release both bimatoprost and NO following instillation into the eye. Bimatoprost, marketed under the brand name LUMIGAN by Allergan, Inc., is the leading product by sales in the class of PGAs, the most widely used class of drugs for IOP-lowering in patients with open-angle glaucoma and ocular hypertension. Bimatoprost is generally considered to be slightly better at lowering IOP than latanoprost.





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Whilst no head-to-head trials have been carried out, we believe that, through the contribution of NO, NCX 470 has the potential for greater IOP lowering activity than bimatoprost.

In December 2018 we entered into an exclusive licensing agreement with Ocumension for the development and commercialization of NCX 470 in the Chinese market. In March 2020 Ocumension's exclusive rights were extended to Korea and South East Asian markets.

### *Top line Results of the Dolomites Phase 2 NCX 470 Clinical Trial*

We completed the randomized, double-masked, dose-response Dolomites Phase 2 trial to determine a concentration of NCX 470 for lowering IOP in patients with open-angle glaucoma or ocular hypertension to advance into further clinical development. The trial enrolled 433 patients across 25 sites in the U.S. Patients were randomized to receive either NCX 470 (0.021%, 0.042% or 0.065%) or latanoprost ophthalmic solution, 0.005% once a day in the evening for 28 days.

All three doses of NCX 470 (0.021%, 0.042%, and 0.065%) met the pre-specified primary efficacy endpoint of non-inferiority to latanoprost for reduction from baseline in mean diurnal IOP at Day 28. In a pre-specified secondary efficacy analysis for reduction from baseline in mean diurnal IOP at Day 28, the mid and high doses of NCX 470 (0.042% and 0.065%) met the secondary efficacy endpoint of statistical superiority to latanoprost based on the trial's pre-specified statistical analysis plan. Specifically, IOP reduction from baseline in mean diurnal IOP at Day 28 was 7.8 mmHg for the 0.021% dose of NCX 470 (p-value for NCX 470 vs. latanoprost not statistically significant); 8.2 mmHg for the 0.042% dose of NCX 470 (p-value for NCX 470 vs. latanoprost=0.0281); and 8.7 mmHg for the 0.065% dose of NCX 470 (p-value for NCX 470 vs. latanoprost=0.0009). The dose-dependent IOP reduction from baseline in mean diurnal IOP at Day 28 showed improved IOP lowering with each incremental concentration of NCX 470 tested, thus creating the potential for additional IOP lowering with a higher concentration of NCX 470.

In additional pre-specified secondary efficacy analysis for reduction from baseline in mean diurnal IOP, NCX 470 (0.065%) met the secondary efficacy endpoint of statistical superiority to latanoprost at Day 7 (p=0.004) and Day 14 (p=0.0174), in addition to Day 28 (p=0.0009; described above). In pre-specified secondary efficacy analyses, the 0.065% dose of NCX 470 showed statistical superiority in IOP lowering as a reduction from baseline at all three time points (8 AM, 10 AM and 4 PM IOPs) on Day 28 compared with latanoprost, with the difference reaching up to 1.4 mmHg (p=0.0214 at 8 AM, p=0.0008 at 10 AM, and p=0.0015 at 4 PM). The IOP lowering effect as reduction from baseline at the three time points (8 AM, 10 AM and 4 PM IOPs) across Day 7, Day 14 and Day 28 ranged from 7.6 to 9.8 mmHg for the 0.065% concentration of NCX 470 compared with 6.3 to 8.8 mmHg for latanoprost. Additionally, at Day 28, 44% of patients dosed with NCX 470 (0.065%) had a 1 mmHg or greater mean diurnal IOP reduction from baseline compared with the mean of 7.4 mmHg for the latanoprost group (p-value not significant); 37% of patients had 2 mmHg or greater reduction (p-value not significant); 27% had a 3 mmHg or greater reduction (p=0.0175); 16% had a 4 mmHg or greater reduction (p=0.0822); and 12% had a 5 mmHg or greater reduction (p=0.0150); compared with the mean for the latanoprost group. Furthermore, greater proportion of patients dosed with NCX 470 (0.065%) achieved a mean diurnal IOP reduction at Day 28 of 40% or greater (p=0.0287), 35% or greater (p=0.0393), 30% or greater (p-value not statistically significant), 25% or greater (p=0.0479) and 20% or greater (p=0.0115), compared with those dosed with latanoprost.

NCX 470 was well tolerated when dosed once daily for 28 days in patients with open-angle glaucoma or ocular hypertension. Only three out of the 433 patients in the trial discontinued due to an adverse event. The majority of adverse events in the trial were mild. The most frequently reported adverse event was conjunctival hyperemia, the majority of which were mild, in 16.8% of patients who dosed with the 0.065% dose of NCX 470 compared with 6.5% of patients who dosed with latanoprost. Notably, adverse events for conjunctival hyperemia plateaued at the 0.042% concentration, for which it was reported for 22.2% of patients. There were no treatment-related serious adverse events, and no evidence of treatment-related systemic side effects.

### *Mont Blanc and Denali Phase 3 Clinical trials*

Nicox successfully completed an End-of-Phase 2 meeting with the U.S. Food and Drug Administration (FDA) and agreed on the design for the NCX 470 Phase 3 program, as well as nonclinical and CMC plans



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supporting submission of a New Drug Application (NDA) in the U.S. On June 1<sup>st</sup>, 2020 Nicox initiated in the U.S. the first Phase 3 clinical trial, Mont Blanc, evaluating NCX 470 for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Mont Blanc is a multi-regional, double-masked, 3-month, parallel group trial evaluating the efficacy and safety of NCX 470 ophthalmic solution, 0.1% compared to latanoprost ophthalmic solution, 0.005% in patients with open-angle glaucoma or ocular hypertension. The 0.1% dose was selected through an initial adaptive portion of the trial. The primary efficacy evaluation of the Mont Blanc trial is based on time-matched IOP at 8 AM and 4 PM at Week 2, Week 6 and Month 3. The Mont Blanc trial is expected to randomize approximately 670 patients at approximately 50 clinical sites, in the U.S. and at a small number of clinical sites in China. Top-line results from Mont Blanc trial are currently expected in H1 2022.

On November 9<sup>th</sup>, 2020 Nicox initiated the second Phase 3 trial in the U.S., Denali, financed jointly and in equal parts by Nicox and Ocumension. Denali is a 3-month Phase 3 trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1% versus latanoprost ophthalmic solution, 0.005%, for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension. The Denali trial, which will also include a long-term safety extension, is expected to randomize approximately 670 patients, at approximately 50 clinical sites in the U.S. and China, with a majority to be recruited in the U.S. The Denali trial, together with the Mont Blanc trial, are designed to fulfill the regulatory requirements to support NDA submissions in the U.S. and China. Top-line results from the Denali trial are currently expected in Q4 2022.

### *NCX 470 Market Research*

In order to understand the potential clinical adoption of NCX 470 for glaucoma and to assess its reimbursement and revenue potential, an independent third party market research agency with extensive experience in the ophthalmology market assessment conducted an initial primary market research trial in the U.S. in the first half of 2019. The market research was comprised of 40 interviews with U.S. ophthalmology key opinion leaders, high volume prescribers including ophthalmologists and optometrists, and third party payers.

Multiple target product profiles of NCX 470 were tested with differentiation from each other by increasing superiority in IOP reduction compared to latanoprost 0.005%, based on a hypothetical statistically significant outcome in a head-to-head Phase 3 clinical trial. The varying levels of efficacy in the three target product profiles tested were chosen based on the current U.S. FDA-approved therapies. Specifically, statistical superiority to latanoprost similar to VYZULTA's published Phase 2 VOYAGER trial was selected for the first profile but with a superior U.S. FDA label based on head-to-head Phase 3 trials vs. PGA for NCX 470, a statistical superiority to latanoprost similar to the published ROCKLATAN Phase 3 Mercury-1 clinical trial at Month 3 but with improved safety and tolerability vs ROCKLATAN was selected for the second profile and finally an ~2 mmHg or better statistical superiority to latanoprost was selected for the third profile. For all three profiles, the safety and tolerability were identical and based on existing PGAs.

Based on our market research, we concluded that there was an opportunity for an impactful product with any of the three profiles tested and that the market potential increased with the size of the improved reduction in IOP. More specifically, the results indicated that the VYZULTA-based product profile had peak U.S. net revenue potential of \$230 million (25% market share of the U.S. first-line therapy branded market); the Mercury-1 ROCKLATAN-based product potential but with improved safety and tolerability to ROCKLATAN had peak U.S. net revenue potential of \$310 million (35% market share of the U.S. first-line therapy branded market); and the profile based on ~2 mmHg superiority to latanoprost had peak U.S. net revenue potential of \$540 million (60% market share of the U.S. first-line therapy branded market). The above forecasts include estimations about the future growth of the market and assume an appropriate level of reimbursement is available.

### *NCX 470 preclinical studies*

In rabbit, dog and non-human primate preclinical models of IOP, our data demonstrate that NCX 470 is able to lower IOP more than bimatoprost alone, with up to 3.5 mmHg greater lowering of IOP with NCX 470 as compared with bimatoprost 0.03% in a non-human primate preclinical model when tested with equimolar solutions (or solutions containing equivalent numbers/concentrations of molecules). Additionally, and notably, in the preclinical model of ocular hypertension in rabbits in which bimatoprost did not have an effect on IOP, NCX 470



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appeared to lower IOP, with up to 8.4 mmHg IOP lowering due to NO alone, suggesting that its NO-donating part of the molecule produces an IOP-lowering action.

### *NCX 4251*

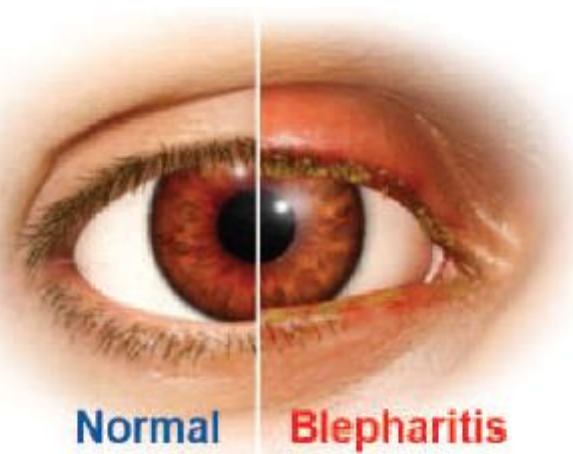
Our second product candidate in clinical development, which leverages an established molecule, is NCX 4251, a novel patented ophthalmic suspension of fluticasone propionate nanocrystals which is being developed as a targeted topical treatment of the eyelids for patients with acute exacerbations of blepharitis. Nicox has completed one Phase 2 trial, Danube with NCX 4251, and is currently in a larger Phase 2b trial, Mississippi, initiated in the U.S. on December 14, 2020 with top-line results currently expected in Q4 2021. We believe that this is the first time that fluticasone propionate is being developed for an ophthalmic indication, and that NCX 4251 is the first product candidate developed as a targeted topical treatment of the eyelids in patients with acute exacerbations of blepharitis. Thus we believe that NCX 4251 may be able to achieve first-in-class status as a treatment for this indication. Blepharitis is a common eye condition characterized by eyelid inflammation. NCX 4251 is being developed for application via an applicator to the eyelids, applied directly to the site where the disease originates and thereby minimizing potential exposure of the drug through the cornea which can lead to the damaging side effects such as IOP increase found with current topical steroids.

In July 2019, we entered into an exclusive license agreement with Ocumension for the development and commercialization of NCX 4251 for blepharitis in the Chinese market.

### *Blepharitis Overview*

Blepharitis is a condition in which the margins of the eyelids become painful, red and swollen and may contain dandruff-like matter, as shown in the picture below, and occurs in two forms. Anterior blepharitis affects the outside front of the eyelids, where the eyelashes are attached, and is most commonly caused by bacteria, demodex (a tiny mite that lives in hair follicles) and scalp dandruff. Posterior blepharitis affects the inner edge of the eyelids, the moist part which makes contact with the tear film of the eye, and is most commonly caused by problems with certain eyelid oil glands, or meibomian glands. Acne, rosacea and scalp dandruff can also cause posterior blepharitis. Both forms of blepharitis are associated with significant inflammation of the eyelid.

An example of the condition is shown in the picture below:



Blepharitis often coexists with other related conditions, such as dry eye, with an incidence that is similar to or higher than dry eye in evaluations of symptomatic patients (24% incidence of blepharitis versus 21% incidence of dry eye). It is believed that in patients with both blepharitis and dry eye, an improvement in blepharitis may lead to an improvement of the dry eye disease. There is not a definitive consensus on the prevalence of the disease. Studies show, however, that blepharitis is one of the most common conditions encountered in clinical practice. Of patients seen by ophthalmologists and optometrists, 37% and 47%, respectively, present with signs of the blepharitis disease.





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There is currently no FDA-approved prescription product solely indicated for blepharitis, which limits our ability to estimate prevalence and market size. There are, however, antimicrobial and antibiotic products, such as ointments and eye drops, indicated for the treatment of blepharitis, as well as other conditions. Treatment options also include lid scrubs, topical ophthalmic steroids, topical ophthalmic antibiotics and topical ophthalmic antibiotic/steroid combinations. We estimate that the market for treatment of acute exacerbations of blepharitis in the U.S. alone may be more than \$700 million, rising to over \$1 billion by 2024. Surveys reveal that ophthalmologists and optometrists consider anti-inflammatory activity to be the most important product attribute when selecting a treatment for blepharitis, which supports the development of NCX 4251.

Fluticasone propionate, the active ingredient in NCX 4251, which has not previously been approved in a topical formulation for use in ophthalmology, has an affinity for the glucocorticoid receptor which is approximately ten times greater than dexamethasone, a corticosteroid commonly used in ophthalmology. Fluticasone is a glucocorticoid with potent anti-inflammatory properties that has been approved in numerous drug products over the past 20 years for the treatment of various indications including dermatology, rhinitis and asthma.

Similar to ZERVATE, we intend to seek regulatory approval for NCX 4251 using the FDA's Section 505(b)(2) regulatory pathway, which enables us to rely, in part, on the FDA's prior findings of safety and efficacy for fluticasone propionate, or published literature, in support of our NDA.

### *Top-line results of the Danube Phase 2 clinical trial*

In December 2019 we completed the U.S. multi-center, randomized, double-masked, placebo-controlled, first-in-man administration, dose-escalation, 14-day Phase 2 clinical trial, Danube, aimed to evaluate the safety and tolerability of NCX 4251 compared to placebo in patients with acute exacerbations of blepharitis. The trial enrolled 36 patients in clinical sites across the U.S. The Danube Phase 2 trial met the primary objective of selecting the dose of NCX 4251 for further development.

NCX 4251 0.1% once daily (QD) treatment was selected to advance into a larger Phase 2 clinical trial.

The selected dose also demonstrated promising efficacy against exploratory endpoints in the study in reducing the signs and symptoms of dry eye disease.

### *Danube Phase 2 clinical trial summary*

All patients in the once daily (n=10 for NCX 4251 and n=5 for placebo) and twice daily (n=10 for NCX 4251 and n=11 for placebo) cohorts successfully completed the 14-day dosing period followed by a 14-day safety evaluation period.

Both once daily (QD) and twice daily (BID) NCX 4251 0.1% were well tolerated. There were no serious adverse events, no treatment related systemic adverse events, and no adverse events of intraocular pressure (IOP) elevation, the most common side effect of topical ophthalmic steroids.

Although the study was not powered for efficacy, in the prospectively defined pooled analysis of QD and BID dosing of NCX 4251 0.1%, there was a statistically significant reduction in the composite score of eyelid redness, eyelid debris and eyelid discomfort at the Day 14 study endpoint (n = 20 for NCX 4251 0.1% and n = 16 for placebo with p = 0.047 for study eyes and p = 0.025 for the combined study eyes and contralateral eyes). Twenty percent of patients on QD dosing of NCX 4251 achieved complete cure, compared to 0% in patients treated with placebo. Due to the small sample size, these results were not statistically significant. Complete cure is defined as a score of zero in eyelid redness, eyelid debris and eyelid discomfort, also referred to as a Composite Score of zero.

Exploratory analyses of signs and symptoms of dry eye disease, including symptom evaluation using visual analog scale and sign evaluation based on corneal and conjunctival fluorescein staining, revealed encouraging reduction from pre-study baselines.



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### *Mississippi Phase 2b clinical trial*

Nicox is conducting the Mississippi Phase 2b clinical trial, a 200 patient trial initiated on December 14, 2020 in the U.S., evaluating once-daily dosed NCX 4251 0.1% versus placebo in patients with acute exacerbations of blepharitis. The primary outcome measure is the proportion of patients achieving complete cure in eyelid redness, eyelid debris and eyelid discomfort, the hallmark signs and symptoms of blepharitis, at Day 15. Top-line results of the Mississippi trial are currently expected in Q4 2021. Should NCX 4251 meet the primary efficacy endpoint for blepharitis, the Mississippi trial could represent the first of two pivotal trials needed to support an NDA for the treatment of blepharitis in the U.S. The Mississippi trial is also designed to assess the impact of NCX 4251 on dry eye signs and symptoms, paving the way for a potential future standalone Phase 3 program in this indication.

### ***NCX 1728 - First in a new class of NO-mediated intraocular pressure lowering agents.***

We are focusing our research efforts on ocular disorders where NO is believed to play a major role in controlling IOP. Our research platform produced the NO-donating compounds, VYZULTA and NCX 470. VYZULTA demonstrated greater IOP lowering than the parent PGA compound in randomized clinical trials. This effect is believed to be due to the additional lowering in IOP from the NO-donating MOA. We are applying key learnings, based on Nicox stand-alone NO-donors, to NO-donating moieties attached to other non-PGA therapeutic classes of compounds with the goal of enhancing the NO-mediated effects. NCX 1728 is the first in a new class of compounds where NO-mediated effects are enhanced by concomitant phosphodiesterase-5 (PDE5) inhibition activity within the same molecule. PDE5 inhibition has been shown both to enhance the efficacy and the duration of nitric oxide-mediated effects. This class has the potential for development alone, as adjunctive therapy or in fixed-dose combinations with latanoprost or other PGAs for lowering IOP in patients with glaucoma or ocular hypertension. NCX 1741, an analog of Nicox's development candidate NCX 1728, demonstrated a reduction of IOP to a similar extent to travoprost, with faster onset of activity. Travoprost is a PGA, a class of molecules which are considered standard of care for IOP lowering in humans.

## **Our Out-Licensed Commercial Products**

### ***VYZULTA—Our Lead Commercial Product***

#### *Overview*

VYZULTA (latanoprostene bunod ophthalmic solution), 0.024% is a PGA with one of its metabolites being NO. At the time of its approval, VYZULTA was the first eye drop approved in twenty years with a novel approach to reduce IOP. VYZULTA was approved by the FDA in November 2017 for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Bausch + Lomb, a leading eye health company, has exclusive worldwide rights to develop and market VYZULTA which is commercialized in the U.S., Canada, Argentina and Mexico and has been also approved in Colombia, Hong Kong, South Korea, Taiwan, Ukraine.

VYZULTA has demonstrated greater IOP lowering at many of the trial's timepoints and a comparable safety profile compared with two currently available medications, latanoprost and timolol, for the lowering of IOP in open-angle glaucoma or ocular hypertension in one Phase 2 clinical trial, and two Phase 3 clinical trials, respectively.

We believe there is an inadequately met or unmet medical need for products with increased IOP lowering in the glaucoma market. We believe that VYZULTA offers a differentiated treatment based on:

- **Increased IOP Lowering**— In the Phase 3 clinical trials, VYZULTA dosed once daily demonstrated statistically significantly greater IOP lowering than twice-daily dosed timolol maleate ophthalmic solution 0.5% throughout the day at three months of treatment. Based on analysis of the pooled results of these trials, the IOP lowering from baseline was in the range of 7.5-9.1 mmHg across three months of treatment. Additionally, in the open-label safety extensions for both Phase 3 trials, VYZULTA demonstrated sustained IOP lowering effect without any loss of efficacy over 12 months (12-month duration of treatment in first Phase 3 trial and 6-month duration of treatment in



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the second Phase 3 trial). In the 413 subject Phase 2 randomized trial, VYZULTA demonstrated statistically significantly greater IOP lowering than latanoprost ophthalmic solution, 0.005% after four weeks of treatment. VYZULTA, the 0.024% dose (N=83), showed statistically significant  $p<0.01$  greater day time IOP lowering from baseline compared with latanoprost at a dose of 0.005% at day 28, with the difference for the 0.024% VYZULTA dose reaching greater than 1 mmHg (statistical significance:  $p<0.01$ ).

- **Novel Dual Mechanism of Action**—VYZULTA is the first PGA approved by the FDA for the lowering of IOP with one of its metabolites being NO and the only once-daily single-agent IOP-lowering product to provide activity through two potential distinct MOAs that are mediated by a prostaglandin and NO.
- **Established Tolerability Profile**—In the Phase 3 clinical trials, 562 patients were exposed to the drug. VYZULTA administered once a day in the evening was well tolerated with no serious adverse events. The most common ocular adverse reactions with incidence  $\geq 2\%$  are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%).

With VYZULTA, increased pigmentation of the iris and eyelid can occur with iris pigmentation likely to be permanent. Gradual changes to eyelashes, including increased length, increased thickness and number of eyelashes, can occur and are usually reversible upon discontinuation of treatment. The most common ocular adverse reactions are conjunctival hyperemia, eye irritation, eye pain and instillation site pain.

### **ZERVIA TE**

#### *Overview*

ZERVIA TE, the brand name for our cetirizine ophthalmic solution, 0.24%, is a novel formulation of cetirizine developed and approved for the first time for topical application in the eye. Cetirizine, the active ingredient in ZYRTEC, is a second generation antihistamine (H1 receptor antagonist) that binds competitively to histamine receptor sites. Cetirizine, in approved oral formulations, has a well-characterized systemic efficacy and safety profile with world-wide exposure resulting from 20 years of oral use. We developed ZERVIA TE as the first and only formulation of cetirizine for topical application in the eye. In May 2017, the FDA approved the NDA for ZERVIA TE for the treatment of ocular itching associated with allergic conjunctivitis.

In September 2017, we entered into an exclusive licensing agreement with Eyevance for the commercialization of ZERVIA TE in the U.S. which is commercialized there since March 2020. In March 2019 we entered into an exclusive licensing agreement with Ocumension for the development and commercialization of ZERVIA TE in the Chinese market. The exclusive rights were expanded to the majority of South East Asian markets in March 2020. Ocumension initiated a Phase 3 clinical trial on ZERVIA TE in China in December 2020. Subject to any additional data requested by the Chinese NMPA, this Phase 3 trial, in addition to the data package used by the FDA for ZERVIA TE in the United States, is expected to be sufficient to support a Chinese NDA.

In December 2019 we entered into an exclusive licensing agreement with Samil for the development and commercialization of ZERVIA TE in South Korea.

In August 2020 we entered into an exclusive licensing agreement with ITROM for the registration and commercialization of ZERVIA TE in Gulf and Arab markets.

The efficacy of ZERVIA TE was established in three Phase 3 trials that were randomized, double-masked, placebo-controlled, conjunctival antigen challenged clinical trials in subjects with a history of allergic conjunctivitis. Onset and duration of action were evaluated in two of these trials, and patients treated with ZERVIA TE demonstrated statistically and clinically significantly less ocular itching compared to its vehicle at 15 minutes and eight hours after treatment ( $p<0.05$ ).



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Regulatory approval for ZERVIAE was obtained via the FDA's Section 505(b)(2) regulatory pathway, which enabled us to rely, in part, on the FDA's prior findings of safety and efficacy for cetirizine and the published literature in support of our NDA.

In seven clinical trials conducted in subjects with allergic conjunctivitis or those at risk of developing allergic conjunctivitis, the most commonly reported adverse reactions occurred in approximately 1% to 7% of subjects treated with either ZERVIAE or vehicle. These reactions were ocular hyperemia, instillation site pain and reduced visual acuity.

### *Allergic Conjunctivitis Overview*

Allergic conjunctivitis occurs when an allergic reaction causes conjunctivitis. Conjunctivitis is an inflammation of the thin layer of tissue that lines the outside of the white surface of the eye and the inner surface of the eyelids. It may affect one or both eyes. The signs and symptoms may include eye redness, excessive watering, itchy burning eyes, discharge, blurred vision and increased sensitivity to light.

It is estimated that more than 75 million people suffer from allergic conjunctivitis in the U.S. and the estimated prevalence of allergic conjunctivitis may be between 15% and 40%. The annual U.S. market for prescription treatment of allergic conjunctivitis totals approximately \$400 million according to IQVIA Health Analytics, which does not include substantial sales of over-the-counter eye drops that we believe are less effective. Branded prescription products represent around 70% market share by value.

### **Non-core partnered program**

#### ***NAPROXCINOD***

Naproxcinod is a Cyclooxygenase-Inhibiting Nitric Oxide-Donating, or CINOD, anti-inflammatory product candidate, which is partnered with Fera Pharmaceuticals in the U.S. Following results from *in vivo* primary pharmacodynamics study of naproxcinod in models of sickle-cell disease, Fera decided to focus its development on the treatment of painful vaso-occlusive crisis in sickle-cell disease. Fera filed an application with the FDA for an Orphan Drug Designation (ODD) for naproxcinod in sickle-cell disease, which was refused. In addition, Fera will evaluate naproxcinod as a potential adjuvant treatment for patients with COVID-19 infection. Subject to successful completion of the ongoing manufacturing of naproxcinod test material, Fera plans to initiate pre-clinical proof-of-concept studies in models of COVID-19 infection in early 2021.

We had previously completed a broad clinical program for naproxcinod in osteoarthritis, including three Phase 3 trials with over 2,700 patients. We submitted an NDA for naproxcinod for osteoarthritis in 2009 and received a Complete Response Letter in 2010 in which the FDA requested substantial additional long-term safety data on the product. We do not plan to further develop naproxcinod for osteoarthritis.

## **5.2 Commercial, Industrial and financial contracts and Intellectual Property**

### **5.2.1 Our Collaboration Agreements**

#### *Bausch + Lomb*

In March 2010, we signed an exclusive worldwide licensing agreement with Bausch + Lomb, a leading eye health company and wholly owned subsidiary of Bausch Health Companies Inc., granting Bausch + Lomb exclusive worldwide rights to develop and market latanoprostene bunod. Latanoprostene bunod is commercialized by Bausch + Lomb under the brand name VYZULTA in the U.S., Canada, Argentina and Mexico and approved in Colombia, Hong Kong, South Korea, Taiwan and Ukraine.

Bausch + Lomb is responsible for funding development and marketing activities, and we jointly manage the collaboration with them through a joint executive committee. The agreement also grants Bausch + Lomb the exclusive worldwide rights to develop and market other products containing latanoprostene bunod, such as fixed-dose combinations, for the reduction of intraocular pressure and/or the treatment of glaucoma.



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Under the terms of the agreement signed in 2010, Bausch + Lomb made an initial license payment of \$10 million to us upon execution of the agreement. Bausch + Lomb made an additional \$10 million milestone payment to us in April 2012 following the decision to pursue further development of latanoprostene bunod after the Phase 2 clinical trial completion in late 2011.

As a result of the FDA's approval of VYZULTA in November 2017, we received a \$17.5 million milestone payment from Bausch + Lomb and we made a \$15 million milestone payment to Pfizer under the 2009 agreement. In March 2018, we and Bausch + Lomb amended the agreement signed in 2010. The amendment provides that, from January 1, 2019 the royalties due to us according to the original agreement will increase by 1% over the original royalty on net sales above \$300 million per year. Royalties will now be 10% to 16% over four tiers, reaching the maximum tier if and when global net sales exceed \$500 million annually. Taking into account our royalty payments to Pfizer, the net royalties to us will be 6% to 12%, compared to 6% to 11% originally. In addition, the potential milestones payable to us by Bausch + Lomb have been increased by \$20 million, added to and split among three existing milestones at increasing annual net sales levels. The first additional amount payable will be added to the milestone on achievement of \$300 million annual net sales and the last additional amount payable will be added to the milestone on achievement of \$700 million annual net sales. The total potential milestones due to us have therefore been increased from \$145 million to \$165 million. The next sales milestone due from Bausch + Lomb remains as originally agreed at \$20 million upon VYZULTA net sales reaching \$100 million, with \$15 million of this milestone paid to Pfizer.

Pursuant to our agreement with Bausch + Lomb, we had an option to co-promote latanoprostene bunod products in the U.S. In August 2014, we informed Bausch + Lomb of our decision to exercise the option. However, we have since agreed with Bausch + Lomb that we will not promote latanoprostene bunod in the U.S.

Additionally, Bausch + Lomb had the option, pursuant to our agreement, to develop additional NO-donating compounds for the reduction of IOP and/or the treatment of glaucoma, including other NO-donating prostaglandin F2-alpha analogs from our research. During the third quarter of 2013, Bausch + Lomb decided to forego this option.

Our licensing agreement with Bausch + Lomb will remain in effect until all royalty payment obligations from Bausch + Lomb expire or unless terminated earlier by either us or Bausch + Lomb pursuant to the early termination provision in the agreement. The duration of royalty obligations under the agreement exists on a country-by-country and licensed product-by-licensed product basis, and commences on the date of first commercial sale for the particular country and the particular licensed product and terminates on the latest of (i) the date on which there exists no subsisting claim of an unexpired patent or collaborative patent covering latanoprostene bunod or a licensed product; (ii) the date of expiration of any period of marketing exclusivity, data protection or data exclusivity applicable to such licensed product in the relevant country; and (iii) ten years after the date of first commercial sale date. If there has been no launch date for a licensed product prior to the expiration of (i) and (ii), the royalty obligation terminates on the later-expiring of (i) and (ii).

We may terminate the agreement on a country-by-country basis if Bausch + Lomb fails to use commercially reasonable efforts to develop and commercialize the licensed products. We may also terminate the agreement in its entirety in the event that Bausch + Lomb challenges or causes a third party to challenge the validity or ownership of any of our licensed patents or fails or becomes unable to meet its payment obligations under the agreement. Bausch + Lomb may terminate this agreement without cause upon 90 days' notice. In the event of termination, except in the event of expiration of the payment obligations of Bausch + Lomb, licenses granted by us to Bausch + Lomb will terminate and any sublicenses granted by Bausch + Lomb will either be assigned to us or terminated.

*Eyevance Pharmaceuticals*

In September 2017, we entered into an exclusive license agreement with Eyevance for the commercialization of ZERVIAE in the U.S.

Under the agreement, Eyevance made a one-time non-refundable upfront payment to us of \$6.0 million in 2017 and a milestone payment \$3.0 million in July 2019 resulting from the achievement by us of certain manufacturing and regulatory objectives. We are eligible to receive up to an additional \$37.5 million in future





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milestones payable on Eyevance achieving pre-defined sales targets, with \$30 million of these milestones being triggered by annual sales targets of \$100 million and above. In addition, we will also receive tiered royalties of 8% to 15% based on future net sales of ZERViate. We also are committed to paying Eyevance consideration related to certain manufacturing costs that resulted from a delay in the completion of certain manufacturing activities which could be up to \$900,000, which will be directly deducted from royalty payments. Nicox may also pay to Eyevance \$250,000 if certain additional manufacturing activities are undertaken by Eyevance.

Eyevance has the exclusive right to commercialize ZERViate in the U.S. where it has been marketed since March 2020. In February 2021, Eyevance has entered into a partnership with Hikma Pharmaceuticals for promoting ZERViate to U.S. healthcare professionals working outside the eyecare specialty, with all sales continuing to be booked by Eyevance, on which Nicox will receive royalties.

The license agreement with Eyevance will remain in force until the later of the fifteenth anniversary of the commercial launch of ZERViate or until the expiry of the last licensed patent in the United States. Eyevance has the right to renew the agreement for two additional five-year periods with three months' advance notice. Additionally, with 90 days' prior written notice, Eyevance can terminate the agreement for convenience and either party can terminate the agreement upon a material breach by the other party following a 90-day cure period. In the event of expiry or termination of the agreement, Eyevance and certain related parties may complete and sell any work-in-process and product inventory that exists as of the date of termination. Upon termination, all rights granted to Eyevance terminate.

*Fera Pharmaceuticals*

In November 2015, we entered into an exclusive license agreement with Fera, granting Fera exclusive rights to develop and commercialize naproxcinod in the United States. The agreement was amended in September 2018 and in December 2020. Fera will evaluate naproxcinod as a potential adjuvant treatment for patients with COVID-19 infection.

Under the terms of the amended agreement, we may be eligible to receive up to \$40 million in a single, one-time only, sales-based milestones if annual sales of naproxcinod reach \$1 billion (in any indication), plus 7% royalties based on net sales of naproxcinod in the U.S. Fera will be responsible for, and will fully finance, all clinical development, manufacturing and commercialization activities. The agreement covers all indications excluding ophthalmology-related conditions and Duchenne Muscular Dystrophy, or DMD, and we will retain all rights for naproxcinod outside of the U.S. Fera is eligible to receive an undisclosed royalty should we sell or license rights to sell naproxcinod or related products in any ex-U.S. territory to a third party if the third party uses any Fera intellectual property, regardless of the therapeutic indication and territory. A joint steering committee will be put in place with representation from both companies to ensure that development of naproxcinod proceeds in accordance with the agreement.

The contract remains in force until the later of the tenth anniversary of the commercial launch or the expiration of the last patent included in the agreement. Upon termination of the agreement due to expiration of the term or our material breach, the licenses become fully paid and irrevocable and Fera will have all rights to the product in the U.S. In the case where Fera, despite having used commercially reasonable efforts, has not submitted an NDA for the product before December 31, 2027, Fera must present a plan for such submission, otherwise we may terminate the agreement. Fera may terminate the agreement at any time by giving one month's notice. In such case (or in the case of material breach by Fera), all the rights concerning regulatory authorizations, intellectual property rights concerning the product and all data (including clinical, preclinical, regulatory, formulation and commercial data) shall be assigned or licensed (if assignment is not possible) to us.



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*ITROM Pharmaceutical Group*

In August 2020 we entered into an exclusive license agreement with ITROM Pharmaceutical Group for the registration and commercialization of ZERVIAE for the treatment of ocular itching associated with allergic conjunctivitis in Gulf and Arab markets including the Kingdom of Saudi Arabia, the United Arab Emirates and Qatar. ITROM is a regional, Dubai-based, internationally recognized pharmaceutical marketing and distribution group of companies specializing in the introduction and representation of breakthrough ophthalmology products since 1999.

Under the terms of the agreement ITROM is granted exclusive rights to develop and commercialize ZERVIAE in Bahrain, Egypt, Iraq, Jordan, Kuwait, Libya, Oman, Qatar, the Kingdom of Saudi Arabia, the United Arab Emirates and Yemen. Nicox is eligible to receive 15% royalties on net sales of ZERVIAE in certain key countries, and 10% in other countries. Nicox will also receive a license fee on signature and may receive a future milestone payment upon product launch. ITROM will be responsible, at its own cost, for development and commercialization of ZERVIAE in the countries of the agreement. ZERVIAE is expected to require only the existing approved U.S. New Drug Application (NDA) package to support approval.

*Ocumension Therapeutics*

In December 2018 we entered into an exclusive license agreement with Ocumension Therapeutics for the development and commercialization of Nicox's product candidate, NCX 470, targeting patients with glaucoma or ocular hypertension for a territory comprising mainland China, Hong Kong, Macau, and Taiwan, or the Chinese market. NCX 470 is currently in two Phase 3 trials, Mont Blanc and Denali, designed to fulfill the regulatory requirements for Phase 3 safety and efficacy trials to support NDA submissions of NCX 470 in the U.S. and China. All development activities are overseen by a Joint Development Committee comprising representatives of both companies, with Ocumension responsible for undertaking all the activities at its own cost. Ocumension received exclusive rights to develop and commercialize NCX 470, at its own cost, in the agreed territory. Under the terms of the agreement, we received a one-time upfront payment of €3 million from Ocumension and Nicox was eligible to receive a further €2.5 million when we initiate a Phase 3 clinical trial with NCX 470 outside the territory of this agreement, and as well to receive up to an additional €14.5 million in milestones associated with Ocumension's progress with NCX 470, up to and including regulatory approval, and up to €16.25 million split over three separate sales milestones associated with potential sales in the territory of up to € 200 million, as well as tiered royalties from 6% to 12% on sales. However, the agreement was amended in March 2020. Ocumension paid Nicox €15 million (in replacement of the totality of the milestones in the original agreement), gained additional exclusive rights to NCX 470 for Korea and South East Asia and will pay 50% of the costs of the second glaucoma Phase 3 clinical trial of NCX 470, Denali. No future NCX 470 milestones will be due from Ocumension to Nicox. In the case that the Joint Trial would not take place, partial or limited refunds of this payment may be made and in certain situations the original milestones of the agreement would again apply. The tiered royalties of 6% to 12% of the original agreement remain unchanged and will apply to sales in the original and the additional territories.

In March 2019 we entered into an exclusive license agreement with Ocumension for the development and commercialization of Nicox's product ZERVIAE for the treatment of allergic conjunctivitis for the Chinese market. All development activities will be overseen by a Joint Governance Committee comprising representatives of both companies, with Ocumension responsible for undertaking all the activities at its own cost. Ocumension received exclusive rights to develop and commercialize ZERVIAE, at its own cost, in the agreed territory. Under the terms of the agreement, we are eligible to receive development and sales milestones of up to €17 million together with royalties of between 5% and 9% on sales of ZERVIAE. The agreement was amended in March 2020 granting Ocumension additional exclusive rights of ZERVIAE in the majority of the Southeast Asian region. Other terms of the original agreement remain unchanged. ZERVIAE is currently in a Phase 3 clinical trial in China.

In June 2019, we entered into an exclusive license agreement with Ocumension for the development and commercialization of Nicox's product candidate, NCX 4251, for blepharitis in the Chinese market. Ocumension is responsible, at its own cost, for all development activities necessary for the approval of NCX 4251 in the territory, overseen by a Joint Development Committee comprising representatives of both companies. Ocumension received exclusive rights for the agreed territory to develop and commercialize NCX 4251 in blepharitis. Under the terms of the agreement, Nicox received an upfront payment of US\$ 2.3 million and may potentially receive



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development and sales milestones of up to US\$ 11.3 million together with tiered royalties of between 5% and 10% on sales of NCX 4251.

### *Pfizer*

In August 2009, we signed an agreement with Pfizer terminating our previous collaboration agreements dated August 2004 and March 2006. Under the terms of the 2009 agreement, we recovered all the development and marketing rights for latanoprostene bunod, and in particular the right to sub-license, as well as all the data and development information. This compound is currently out-licensed to Bausch + Lomb (see above). Moreover, we also have access to certain information regarding development of XALATAN (latanoprost ophthalmic solution) 0.005% belonging to Pfizer, in particular the regulatory files for XALATAN (latanoprost ophthalmic solution) 0.005%. In return, we are obligated to pay Pfizer two milestone payments of \$15 million each linked to approval of VYZULTA in the U.S. (or a lower amount if approved only in Europe or Japan) and \$15 million linked to reaching predefined sales levels. The first milestone payment was made in December 2017. Pfizer is also entitled to receive royalties on potential future sales. Pfizer's royalties are in the low single digit percentages for sales in the U.S. and sales made directly by us outside the United States. For sales made by our licensees outside the U.S., Pfizer's royalty is the greater of our royalty rate for sales outside the U.S. or a low double-digit percentage of the income that we receive from such licensee. We also recovered the rights to a certain number of new NO donors at the research stage for the potential treatment of diabetic retinopathy and glaucoma.

### *Samil Pharmaceutical*

In December 2019 we entered into an exclusive license agreement with Samil Pharmaceutical Co., Ltd, or Samil, for the development and commercialization of ZERVIAE (cetirizine ophthalmic solution), 0.24% for the treatment of ocular itching associated with allergic conjunctivitis in South Korea. Samil is considered as one of the leading Korean companies specialized in the field of ophthalmic medicines including the research and development of drugs in the field of ophthalmology.

Samil will receive exclusive rights to develop and commercialize ZERVIAE in South Korea, where the market for allergic conjunctivitis was worth nearly €31 million for the 12 months to Q3 2019. Nicox is eligible to receive 10% royalties on net sales on ZERVIAE in South Korea and a milestone payment of 5% of net sales for each calendar year in which net sales exceed approximately US\$900,000 (at current exchange rates). Nicox will also receive a license fee, and may receive approval and launch milestone payments which, together with the license fee, may total almost US\$250,000. Samil will be responsible, at its cost, for development and commercialization of ZERVIAE in South Korea. ZERVIAE is expected to require only manufacturing transfer and associated pharmaceutical development to support approval in South Korea, in addition to the existing approved U.S. NDA package.

### **5.2.2 Other Partnerships**

We have other partnerships that are not active at this time. For instance, under our collaboration with Portola Pharmaceuticals, Inc., we have exclusive rights to jointly develop certain of their preclinical small molecules for topical ophthalmic indications, but no compound has been selected for development under this agreement. Under our collaboration with Merck, Merck can elect to develop certain of our NO-donating compounds in the cardiovascular field. We do not expect these partnerships to impact our future financial status at this time.

### **5.2.3 Manufacturing and Supply**

We do not have any in-house manufacturing facilities or logistics platforms. Therefore, we need to secure agreements with third parties for the manufacturing and supply of our product candidates under development. These third parties either manufacture and assemble in-house or outsource one or more processes to other external service providers.

Our business is subject to risks associated with our reliance on third-party suppliers. These risks are discussed more fully in the section of this prospectus titled "Risk Factors."





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### **5.3 Patents**

#### **5.3.1 Industrial property protection policy**

Intellectual property is of vital importance to the Company's businesses. Nicox takes all possible measures to protect intellectual property, including by obtaining and maintaining patent protection in different territories (particularly in the United States) for its products under development and other inventions important for its business. The Group must also use of trade secrets to protect and ensure the confidentiality of proprietary information to protect those aspects of its business operations that do not lend themselves to patent protection or considered by Nicox as not appropriate for patent protection. The Company must also have recourse to the filing of trademarks, copyrights and contractual obligations to establish and protect its intellectual property rights.

Nicox's activities are dependent on its intellectual property and as such are subject to risks linked to the uncertain protection offered by patents and other intellectual property rights. The position of pharmaceutical companies like Nicox with respect to patents is highly uncertain and involves extremely complex legal, scientific and factual circumstances. In addition, the protections sought in patent applications may be significantly reduced before the patent is issued and its scope may be reinterpreted after it is issued. For that reason, the possibility cannot be excluded that Nicox might not be successful in obtaining or maintaining a patent protection for one of its products under development. The Company cannot anticipate if the patent applications currently pending will result in the issuance of patents in all the targeted territories, or if the claims of the patents issued will offer sufficient protection against the competition. Any patent held by the Company may be challenged, circumvented or invalidated by third parties. The reader is invited to refer to section 3 “risk factors” of the universal registration document that describes the risk factors related to the uncertain protection provided by patents and other intellectual property rights.

The Group has a patent department within its Italian subsidiary Nicox Research Institute Srl. The Group's patent department regularly uses industrial property law firms in several countries around the world.

Nicox also relies on trade secret protection for its confidential and proprietary information. Even though the Group takes measures to protect its proprietary information and trade secrets, including through contractual provisions with its employees and consultants, third parties may develop independently information and proprietary techniques substantially equivalent or gain access to its trade secrets or disclose its technology. For those reasons, Nicox might not be able to effectively protect its trade secrets. The company's policy requires staff, consultants, external scientific staff and other consultants to sign confidentiality agreements at the start of their employment or relations as consultants with Nicox. The agreements thus concluded with employees also provide that all inventions designed by an employee in the course of his or her term of employment within the Company or based on the use of confidential information of the Company remain the exclusive property of Nicox.

#### **5.3.2 Nature and coverage of patent families owned by the company**

As of December 31, 2020, our patent portfolio included 322 issued patents and 79 pending patent applications and 3 patent applications under the Patent Cooperation Treaty, or PCT. In the U.S., our patent portfolio includes 42 issued patents and 9 pending patent applications. We also have 17 patents granted by the European Patent Office, which have been validated in the principal European countries, and 7 pending European patent applications.

Latanoprostene bunod (the active ingredient of VYZULTA) is protected in the United States by four granted patents which expire in 2025. A patent term extension (PTE) application was filed in December 2017. If this Patent Term Extension (PTE) is accepted, it could provide additional protection until 2030.

In Europe, a patent covering latanoprostene bunod (the active ingredient of VYZULTA) was issued in February 2016 and validated in 36 countries of the EPC (European Patent Convention) and will provide protection until 2024. An application could be made for a Supplementary Protection Certificate (SPC) to extend the term of the patent to a maximum of 5 years.

On November 23, 2016, Teva Pharmaceutical Industries Ltd. filed a notice of opposition against the grant of the European patent covering latanoprostene bunod. On July 13, 2018, the Opposition Division rejected the



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opposition and decided to maintain the patent as granted. On September 12, 2018, Teva Pharmaceutical Industries Ltd. filed an appeal against the decision of the Opposition Division. In March 2019, Nicox filed its statement of appeal. The date this appeal decision will be rendered is not known on this date.

In Japan, latanoprostene bunod (the active ingredient of VYZULTA) is protected by a patent which expires in 2024.

ZERVIAE is protected in the United States by four patents expiring in 2030 and 2032. In Europe a patent application is currently under examination. If issued, this patent will offer protection until 2030.

In Japan, ZERVIAE is covered by two patents expiring in March 2030.

NCX 4251 is protected in the United States and in Europe by patents which expire in 2033. In Europe.

In July 2020, Nicox filed a PCT application and national patent applications in the U.S., Europe (EPC), China, Japan, Taiwan and Argentina covering the process for the preparation of the NCX 4251 formulation under development and the NCX 4251 formulation as product; this patent family, if granted, will provide worldwide patent coverage until 2040.

NCX 4240 is protected in the United States, Japan and Mexico by granted patents covering the NCX 4240 eyedrop formulation and its therapeutic use for treating specific viral infections of the eye. In Canada the patent application is under review. These patents will provide protection until 2035.

NCX 470 is covered by a patents family which includes the granted patent US 8,101,658 expiring in 2029 and the European patent EP 2 274 279 which was validated in France, Germany, Italy, Spain and the United Kingdom. The product patent family also includes patents granted in Canada, Japan, China, Hong Kong, Argentina and India which are in force until 2029. Patent US 8,101,658 is eligible for a patent term extension which, if granted, may extend the expiration date for a period of up to five years.,

In July 2019, Nicox filed a PCT application and national patent applications in USA, Europe (EPC), China, Japan, Taiwan and Argentina covering the NCX 470 formulation under development. In 2020, the U.S., the European and the Japanese patents were granted extending patent coverage of the NCX 470 formulation to 2039.

In February 2019, Nicox filed a PCT application and other national patent applications covering an industrial process of synthesis of NCX 470. These patent applications, if granted, will provide worldwide patent coverage for NCX 470 until 2039 - 2040. In Europe a patent was granted in September 30th, 2020 and it was validated in 14 member States of the European Patent Convention (EPC).

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing a non-provisional patent application.

In the United States, the patent term of a patent that covers an FDA-approved drug may also be eligible for patent term extension, which permits patent term restoration as compensation for the patent term lost during the FDA regulatory review process. The Hatch-Waxman Act permits a patent term extension of up to five years beyond the expiration of the patent.

The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only one patent applicable to an approved drug may be extended. Similar provisions are available in Europe and other foreign jurisdictions. In the future, if our products receive FDA approval or other regulatory authorities, we expect to apply for patent term extensions on patents covering one or more of those products. However, there is no guarantee that the applicable authorities will agree with our assessment of whether such extensions should be granted and, if granted, the length of such extensions.

The following tables summarize the status of our current patent portfolio for Nicox products and key product candidates as of December 31, 2020. For each family of patents, a table shows the different members of the family in force, by country, with the maximum possible expiration date subject to regular payment of maintenance fees and the absence of questioning of the validity of the patent concerned.



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**VYZULTA (latanoprostene bunod)**

**Patent title: PROSTAGLANDIN DERIVATIVES**

This patent family covers nitrooxy-derivatives of prostaglandin F2 $\alpha$  analogues having improved pharmacological activity and enhanced tolerability and their use for the treatment of glaucoma and ocular hypertension.

Latanoprostene bunod, its use for the treatment of glaucoma and ocular hypertension and its pharmaceutical formulations are specifically disclosed and claimed.

**Patent owner:** Nicox SA

<b>Patent status</b>	<b>Territory</b>		<b>Filing Date</b>	<b>Issue Date</b>	<b>Expiry date*</b>
Granted	Europe#	EP 1 704 141	27-Dec-2004	24-Feb-2016	27-Dec-2024
		US 7,273,946^	05-Jan-2005	25-Sep-2007	03-Oct-2025
	United States	US 7,629,345^	05-Jan-2005	08-Dec-2009	05-Jan-2025
		US 7,910,767^	05-Jan-2005	22-Mar-2011	05-Jan-2025
		US 8,058,467^	05-Jan-2005	15-Nov-2011	05-Jan-2025
		JP 3 984 283	27-Dec-2004	13-July-2007	27-Dec-2024
	39 other countries		Dec-2004 - Jan-2005	Aug-2006 - Feb-2016	Dec-2024 - 5-Jan-2025
Pending	Europe	EP3643702 A1	9-sep-2019	—	27-Dec-2024
	7 other countries		27-Dec-2004	—	27-Dec-2024

(\*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(#) EP 1 704 141 was validated in 36 member States of the European Patent Convention (EPC). On November 23, 2016, TEVA Pharmaceutical Industries Ltd, or TEVA, filed a Notice of Opposition at the EPO. On July 13, 2018, the Opposition Division decided to reject the Opposition and to maintain the patent as granted. A notice of appeal against the decision of the Opposition Division was filed by TEVA Pharmaceutical Industries Ltd on September 12, 2018. On March 2019, Nicox filed a reply to the grounds of appeal. Appeal decision is still pending.

(^ ) U.S. 7,273,946, U.S. 7,629,345, U.S. 7,910,767 and U.S. 8,058,467 are listed in the Orange Book for VYZULTA.

In December 2017, Nicox filed requests for PTE for U.S. 7,273,946, U.S. 8,058,467 and U.S. 7,629,345 at the USPTO.



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**ZERVIA TE (cetirizine)**

**Patent title: OPHTHALMIC FORMULATIONS OF CETIRIZINE AND METHOD OF USE**

This patent family covers topical ophthalmic formulations comprising cetirizine and its salts wherein cetirizine is present in an amount of 0.1% to 0.25% (w/v), and method for alleviating signs and symptoms of allergic conjunctivitis by topical administration of the ophthalmic formulations.

ZERVIA TE, 0.24% cetirizine hydrochloride formulation and its use in the treatment of ocular itching associated with allergic conjunctivitis are specifically claimed.

**Patent owner:** Nicox Ophthalmics Inc.

<b>Patent status</b>	<b>Territory</b>		<b>Filing Date</b>	<b>Issue Date</b>	<b>Expiry date*</b>
Granted	United States	US 9,254,286 <sup>^</sup>	15-March-2010	9-Feb-2016	09-July-2032
		US 8,829,005 <sup>^</sup>	21-May-2013	9-Sep-2014	15-March-2030
		US 9,750,684 <sup>^</sup>	29-Dec-2015	05-Sept-2017	15-March-2030
		US 9,993,471 <sup>^</sup>	29-Dec-2015	12-June-2018	15-March-2030
	Japan	JP 6033677	15-March-2010	04-Nov-2016	15-March-2030
		JP 6144393	12-Aug-2016	19-May-2017	15-March-2030
	other country	CA 2,755,679	15-March-2010	12-Sept-2017	15-March-2030
Pending	Europe	EP 2 408 453 A	15-March-2010	—	15-March-2030
	United States	US 2020/0405711	11-Sept-2020	—	15-March-2030

(\*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(<sup>^</sup>) U.S. 9,254,286, U.S. 8,829,005, U.S. 9,750,684 and U.S. 9,993,471 are listed in the Orange Book for ZERVIA TE.



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**NCX 470 (NO-donating bimatoprost)**

**Patent title: NITRIC OXIDE DONATING PROSTAMIDES**

This patent family covers nitrooxy-derivatives of bimatoprost and their use for treating glaucoma and ocular hypertension.

NCX 470 is specifically disclosed and claimed.

**Patent owner:** Nicox SA

<b>Patent status</b>	<b>Territory</b>		<b>Filing Date</b>	<b>Issue Date</b>	<b>Expiry date*</b>
Granted	Europe#	EP 2 274 279	11-May-2009	31-July-2013	11-May-2029
	United States	US 8,101,658	11-May-2009	24-Jan-2012	11-May-2029
	Japan	JP 5 401 540	11-May-2009	01-Nov-2013	11-May-2029
	China	CN102099330	11-May-2009	30-Apr-2014	11-May-2029
	4 other countries		11-May-2009	2015 - 2019	11-May-2029

(\*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(#) EP 2 274 279 was validated in five main European countries.

**NCX 470 eyedrop formulation**

**Patent title: OPHTHALMIC COMPOSITIONS CONTAINING A NITRIC OXIDE RELEASING PROSTAMIDE**

This patent family covers aqueous ophthalmic compositions in the form of solution containing NCX470 and macrogol 15 hydroxystearate as the only solubilizing agent, and a method for their preparation.

**Patent owner:** Nicox SA

<b>Patent status</b>	<b>Territory</b>		<b>Filing Date</b>	<b>Issue Date</b>	<b>Expiry date*</b>
Active	PCT§	WO2020/011845	10-July-2019	NA	
Granted	Europe#	EP 3 583 788#	10-July-2019	28-Oct-2020	10-July-2039
	United States	US 10,688,073	10-July-2019	23-June-2020	10-July-2039
	Japan	JP 6672512	10-July-2019	6-March-2020	10-July-2039
	Europe	EP20172140.4	29-Apr-2020	-	10-July-2039
Pending	United States	US 2020/0206176	11-Mar-2020	-	10-July-2039
	China	CN201910622356.1	10-July-2019	-	10-July-2039
	China	CN 111249228A	4-Mar-2020	-	10-July-2039
	Japan	JP 2020-105201 A	4-Mar-2020	-	10-July-2039
	3 other countries		10-July-2019	-	10-July-2039

(\*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(#) EP 3 583 788 will be validated in 42 member States of the European Patent Convention (EPC).

(§) PCT/ WO2020/011845 will enter the national phases in January 2021

In February 2019, Nicox filed a PCT application and national patent applications in Taiwan and Argentina covering an industrial process of synthesis of NCX 470. This patent family, if granted, will provide worldwide patent coverage until 2039. In Europe a patent was granted in September 30, 2020 and it was validated in 14 member States of the European Patent Convention (EPC)



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**NCX 4251 (Fluticasone propionate nanocrystals)**

**Patent title:** PREPARATION OF HYDROPHOBIC THERAPEUTIC AGENTS, METHOD OF MANUFACTURE AND USE THEREOF

This patent family covers nanocrystals of Fluticasone propionate (Form A) wherein the nanocrystals have the c-axis crystallographic direction normal to the surfaces that define the thickness of the nanocrystals and an average particle size of 100 nm to 1000 nm.

This patent family also covers: nanosuspensions containing nanocrystals of Fluticasone propionate (Form A), methods for treating or alleviating symptoms of blepharitis, post-operative ocular inflammation, dry eye or eye allergy and the sonocrystallization process for preparing the Fluticasone propionate nanocrystals.

**Patent owner:** Nicox Ophthalmics Inc.

Patent status	Territory		Filing Date	Issue Date	Expiry date*
Granted	United States	US 8,765,725	07-Jan-2013	01-July-2014	7-Jan-2033
	United States	US 10,174,071	26-July-2018	8-Jan-2019	6-May-2033
	Japan	JP 6285419	06-May-2013	09-Feb-2018	6-May-2033
	Japan	JP 6564891	01-Feb-2018	2-Aug-2019	6-May-2033
	Japan	JP 6752940	17-June-2019	21-Aug-2020	6-May-2033
	Europe	EP 2 847 207^	06-May-2013	27-March-2019	6-May-2033
	Europe	EP 3517541#	11-Feb-2019	15-July-2020	6-May-2033
	China	CN 107880091	23-Nov-2017	18-Dec-2020	6-May-2033
	7 other countries		06-May-2013	2018-2020	6-May-2033
	Pending	Europe	EP 3 741 772 A1	29-May-2020	—
United States		US 2019/0169224	29-Nov-2018	—	6-May-2033
6 other countries					

(\*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.

(^ ) EP 2 847 207 was validated in 12 member States of the European Patent Convention (EPC)

(#) EP 3 517 541 was validated in 24 member States of the European Patent Convention (EPC)

**NCX 4280 (formerly AC-120)**

**Patent title:** METHOD FOR THE TREATMENT AND PREVENTION OF EYELID SWELLING

This patent family covers the use of a composition comprising oxymetazoline and glycerine for treating eyelid swelling.

This patent family also discloses topical pharmaceutical compositions comprising an osmotically active agent and a vasoconstrictor agent. The preferred osmotically active agent is glycerin and the vasoconstrictor agent is selected from oxymetazoline or naphazoline.

**Patent owner:** Nicox Ophthalmics Inc.

<u>Patent status</u>	<u>Territory</u>		<u>Filing Date</u>	<u>Issue Date</u>	<u>Expiry date*</u>
Granted .....	United States	US 8,685,439	26-Apr-2007	01-Apr-2014	09-July-2030
Pending .....	United States	US 14/178,846	12-Feb-2014	—	26-Apr-2027
		US 15/366,559	01-Dec-2016	—	26-Apr-2027

(\*) Expiry dates given prior to any potential extensions in accordance with local patent regulations.





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**Protection for other NO-donating compounds**

Our novel NO-donating PDE5 inhibitors have potential patent protection in the United States, Europe and other main countries until 2039. Additional novel molecules combining NO-donation and other non-PGA MOAs compounds are protected in the United States, Europe and other main countries by patents and patent applications that provide patent protection until 2034.

**5.4 Important events**

**5.4.1 Important events since January 1<sup>st</sup>, 2020**

January 13, 2020: **Nicox's Partner Secures Approval of VYZULTA® in Mexico**

[https://www.nicox.com/assets/files/EN\\_VYZULTA-Mexico-approval\\_20200113\\_F1.pdf](https://www.nicox.com/assets/files/EN_VYZULTA-Mexico-approval_20200113_F1.pdf)

January 16, 2020: **Nicox's Partner Secures Additional Approvals of VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% in Hong Kong and Argentina**

[https://www.nicox.com/assets/files/EN\\_VYZULTA-HK-and-Argentina-PR\\_20200116-F2.pdf](https://www.nicox.com/assets/files/EN_VYZULTA-HK-and-Argentina-PR_20200116-F2.pdf)

January 21, 2020: **Nicox Fourth Quarter 2019 Business Update and Financial Highlights**

[https://www.nicox.com/assets/files/EN\\_Q4\\_2019\\_RESULTS\\_F\\_20200121.pdf](https://www.nicox.com/assets/files/EN_Q4_2019_RESULTS_F_20200121.pdf)

February 3, 2020: **Nicox Receives Formulation Patent Extending NCX 470 U.S. Patent Coverage to 2039**

[https://www.nicox.com/assets/files/EN\\_NCX470\\_USFORMULATIONPATENTPR\\_20200203\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX470_USFORMULATIONPATENTPR_20200203_F.pdf)

March 5, 2020: **Nicox's Positive End-of-Phase 2 Meeting with the U.S. FDA Sets Stage for NCX 470 Phase 3 Program in Glaucoma**

[https://www.nicox.com/assets/files/EN\\_NCX470\\_FDAEOP2\\_PR\\_20200305\\_F1.pdf](https://www.nicox.com/assets/files/EN_NCX470_FDAEOP2_PR_20200305_F1.pdf)

March 6, 2020 **Nicox Announces 2019 Financial Results and 2020 Key Milestones**

[https://www.nicox.com/assets/files/EN\\_2019-YE-results\\_-20200306\\_F1.pdf](https://www.nicox.com/assets/files/EN_2019-YE-results_-20200306_F1.pdf)

March 9, 2020 **Nicox's Partner Secures Additional Approval of VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024% in Taiwan**

[https://www.nicox.com/assets/files/EN\\_VYZULTA\\_TAIWAN\\_APPROVAL\\_PR\\_20200309\\_F.pdf](https://www.nicox.com/assets/files/EN_VYZULTA_TAIWAN_APPROVAL_PR_20200309_F.pdf)

March 11, 2020 **Nicox Updates on ZERVIAE™ Progress in China and Expands the Countries of its Agreement with Ocumension Therapeutics**

[https://www.nicox.com/assets/files/EN\\_OCUMENSION\\_ZERVIAE\\_AMENDMENT\\_20200311\\_F.pdf](https://www.nicox.com/assets/files/EN_OCUMENSION_ZERVIAE_AMENDMENT_20200311_F.pdf)

March 11, 2020 **Nicox to Receive €15 Million and Half of the Cost of the Second NCX 470 Phase 3 Clinical Trial from Ocumension Therapeutics under Amended Agreement**

[https://www.nicox.com/assets/files/EN\\_OCUMENSION\\_NCX470\\_JOINT\\_TRIAL\\_20200311\\_F.pdf](https://www.nicox.com/assets/files/EN_OCUMENSION_NCX470_JOINT_TRIAL_20200311_F.pdf)

March 31, 2020 **Nicox Announces ZERVIAE™ Launch by Partner Eyeevance Pharmaceuticals in the United States**

[https://www.nicox.com/assets/files/EN\\_ZERVIAE-U.S.-LAUNCH-PR\\_-20200331\\_F1.pdf](https://www.nicox.com/assets/files/EN_ZERVIAE-U.S.-LAUNCH-PR_-20200331_F1.pdf)



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April 2, 2020 **Nicox's Partner Fera Pharmaceuticals Files Application for Orphan Drug Designation for Naproxinod in Sickle-Cell Disease**

[https://www.nicox.com/assets/files/EN\\_Fera\\_SickleCell\\_PR\\_20200402\\_F.pdf](https://www.nicox.com/assets/files/EN_Fera_SickleCell_PR_20200402_F.pdf)

April 8, 2020 **Nicox Outlines Plans to Progress NCX 4251 into Phase 2b Trial Following Positive Meeting with FDA**

[https://www.nicox.com/assets/files/EN\\_NCX-4251-FDA-MEETING\\_20200408\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX-4251-FDA-MEETING_20200408_F.pdf)

April 17, 2020 **Nicox First Quarter 2020 Business Update and Financial Highlights**

[https://www.nicox.com/assets/files/EN\\_Q1-2020-results-\\_20200417\\_F.pdf](https://www.nicox.com/assets/files/EN_Q1-2020-results-_20200417_F.pdf)

June 2, 2020 **Nicox Initiates First Phase 3 Trial of NCX 470 in Glaucoma**

[https://www.nicox.com/assets/files/EN\\_NCX-470\\_Mont-Blanc-FPFV\\_PR\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX-470_Mont-Blanc-FPFV_PR_F.pdf)

July 10, 2020 **Nicox Strengthens Cash Position With Divestment of its VISUfarma Shareholding**

[https://www.nicox.com/assets/files/EN\\_VISUFARMA\\_STAKE\\_SALE\\_PR\\_20200710\\_F-.pdf](https://www.nicox.com/assets/files/EN_VISUFARMA_STAKE_SALE_PR_20200710_F-.pdf)

July 10, 2020 **Nicox Partner Ocumension Completes Successful Hong Kong IPO at an approximately US\$1,090 Million Valuation**

[https://www.nicox.com/assets/files/EN\\_OCUMENSION\\_POST-IPO\\_PR\\_20200710\\_F1.pdf](https://www.nicox.com/assets/files/EN_OCUMENSION_POST-IPO_PR_20200710_F1.pdf)

July 15, 2020 **Nicox Reports on Enrollment Progress in Mont Blanc Phase 3 Clinical Trial in Glaucoma**

[https://www.nicox.com/assets/files/EN\\_NCX-470-Phase-3-enrollment-PR-\\_20200715.pdf](https://www.nicox.com/assets/files/EN_NCX-470-Phase-3-enrollment-PR-_20200715.pdf)

July 17, 2020 **Nicox Second Quarter 2020 Business Update and Financial Highlights**

[https://www.nicox.com/assets/files/EN\\_Q2\\_2020\\_results-\\_PR\\_20200717\\_F1.pdf](https://www.nicox.com/assets/files/EN_Q2_2020_results-_PR_20200717_F1.pdf)

July 31, 2020 **Nicox Receives €5 Million Upon Closing of VISUfarma Divestment**

[https://www.nicox.com/assets/files/EN\\_CLOSING\\_SALE\\_VISUFARMA\\_STAKE\\_PR\\_F.pdf](https://www.nicox.com/assets/files/EN_CLOSING_SALE_VISUFARMA_STAKE_PR_F.pdf)

August 5, 2020 **Nicox: Implementation of a liquidity contract with Kepler Cheuvreux**

[https://www.nicox.com/assets/files/EN\\_Kepler-liquidity-contract-2020-PR\\_20200805\\_F.pdf](https://www.nicox.com/assets/files/EN_Kepler-liquidity-contract-2020-PR_20200805_F.pdf)

August 5, 2020 **Nicox Negotiating €2 million Non-Dilutive Loans Guaranteed by the French State**

[https://www.nicox.com/assets/files/EN\\_PGE-confirmation-PR-August-5-F.pdf](https://www.nicox.com/assets/files/EN_PGE-confirmation-PR-August-5-F.pdf)

August 12, 2020 **Nicox Partners ZERVIA<sup>TM</sup> in the Gulf and Arab Markets**

[https://www.nicox.com/assets/files/EN\\_ZERVIA ITROM LICENSE AUGUST2020\\_P R\\_F.pdf](https://www.nicox.com/assets/files/EN_ZERVIA ITROM LICENSE AUGUST2020_P R_F.pdf)

September 2, 2020 **Nicox Completes Enrollment of the Adaptive Design Cohort of NCX 470 Mont Blanc Phase 3 Glaucoma Trial**

[https://www.nicox.com/assets/files/EN\\_NCX-470-Ph3\\_adaptive-cohort\\_20200902\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX-470-Ph3_adaptive-cohort_20200902_F.pdf)

September 10, 2020 **Nicox First Half 2020 Financial Results and Business Update**





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[https://www.nicox.com/assets/files/EN\\_H1-2020results\\_20200910\\_F2\\_F.pdf](https://www.nicox.com/assets/files/EN_H1-2020results_20200910_F2_F.pdf)

September 18, 2020 **Nicox Announces Senior Management Change**  
[https://www.nicox.com/assets/files/EN\\_TNDepartureSept2020\\_PR\\_20200918\\_F.pdf](https://www.nicox.com/assets/files/EN_TNDepartureSept2020_PR_20200918_F.pdf)

September 22, 2020 **Nicox's ZERVIA<sup>TM</sup> Receives IND Approval in China**  
[https://www.nicox.com/assets/files/EN\\_ZERVIAChineseINDApproval\\_20200922\\_F.pdf](https://www.nicox.com/assets/files/EN_ZERVIAChineseINDApproval_20200922_F.pdf)

September 23, 2020 **Nicox Selects 0.1% NCX 470 Dose in Adaptive Stage of Mont Blanc Phase 3 Glaucoma Trial**  
[https://www.nicox.com/assets/files/EN\\_NCX470\\_AdaptiveDesignDoseSelection\\_PR\\_20200923\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX470_AdaptiveDesignDoseSelection_PR_20200923_F.pdf)

September 24, 2020 **Bausch Health Announces VYZULTA<sup>®</sup> (latanoprostene bunod ophthalmic solution), 0.024%, is now approved in seven countries**  
[https://www.nicox.com/assets/files/EN\\_VYZULTA-Approved-in-Seven-Countries\\_20200924\\_F1.pdf](https://www.nicox.com/assets/files/EN_VYZULTA-Approved-in-Seven-Countries_20200924_F1.pdf)

October 13, 2020 **Nicox Announces Plans for NCX 4251 Phase 2 Trial in Blepharitis**  
[https://www.nicox.com/assets/files/EN\\_NCX4251Phase2TrialDesign\\_PR\\_20201013\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX4251Phase2TrialDesign_PR_20201013_F.pdf)

October 20, 2020 **Nicox Announces Third Quarter 2020 Business Update and Financial Highlights**  
[https://www.nicox.com/assets/files/EN\\_Q3ResultsOctober2020\\_PR\\_20201020\\_F.pdf](https://www.nicox.com/assets/files/EN_Q3ResultsOctober2020_PR_20201020_F.pdf)

October 23, 2020 **Nicox Selects Development Candidate in a New Class of NO-mediated Intraocular Pressure (IOP)**  
[https://www.nicox.com/assets/files/EN\\_NCX-1728-selection-PR\\_20201023\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX-1728-selection-PR_20201023_F.pdf)

Lowering Agents

October 26, 2020 **Nicox's NCX 470 Receives Approval by Chinese Authorities for Local Start of Mont Blanc Phase 3 Trial**  
[https://www.nicox.com/assets/files/EN\\_NCX470Chinese-IND-Approval-PR\\_20201026\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX470Chinese-IND-Approval-PR_20201026_F.pdf)

October 29, 2020 **Nicox Granted New Patent for NCX 470, Extending Exclusivity in Europe to 2039**  
[https://www.nicox.com/assets/files/EN\\_NCX-470-EUFormulation-Patent-Approval-PR\\_20201029\\_F1-1.pdf](https://www.nicox.com/assets/files/EN_NCX-470-EUFormulation-Patent-Approval-PR_20201029_F1-1.pdf)

November 10, 2020 **Nicox Initiates Second Phase 3 Trial of NCX 470 in Glaucoma**  
[https://www.nicox.com/assets/files/EN\\_NCX470-Denali-Phase-3-Start-PR\\_20201110\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX470-Denali-Phase-3-Start-PR_20201110_F.pdf)

November 23, 2020 **Nicox's Licensee Bausch + Lomb Launches VYZULTA<sup>®</sup> in Argentina**  
[https://www.nicox.com/assets/files/EN\\_VYZULTA-Argentina-Launch\\_20201123\\_F.pdf](https://www.nicox.com/assets/files/EN_VYZULTA-Argentina-Launch_20201123_F.pdf)

November 25, 2020 **Nicox Analyst Coverage Initiated by Kepler Cheuvreux**  
[https://www.nicox.com/assets/files/EN\\_Kepler-coverage-initiation\\_VF.pdf](https://www.nicox.com/assets/files/EN_Kepler-coverage-initiation_VF.pdf)



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- December 11, 2021 **Nicox's Partner Fera Pharmaceuticals to Investigate Naproxcinod as Potential Covid-19 Adjuvant Treatment**  
[https://www.nicox.com/assets/files/EN\\_FeraNaproxcinodCOVID\\_PR\\_F.pdf](https://www.nicox.com/assets/files/EN_FeraNaproxcinodCOVID_PR_F.pdf)
- December 15, 2021 **Nicox Initiates Phase 2b Trial of NCX 4251, a Potential First-in-Class Treatment for Blepharitis**  
[https://www.nicox.com/assets/files/EN\\_NCX4251-Mississippi-Phase-2b-Start\\_PR\\_20201215\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX4251-Mississippi-Phase-2b-Start_PR_20201215_F.pdf)
- December 22, 2021 **Nicox's Licensee Bausch + Lomb Secures Approval of VYZULTA® in Colombia**  
[https://www.nicox.com/assets/files/EN\\_VYZULTA-approval-Colombia\\_20201222\\_F.pdf](https://www.nicox.com/assets/files/EN_VYZULTA-approval-Colombia_20201222_F.pdf)
- December 30, 2021 **Nicox's Partner Ocumension Therapeutics Initiates ZERVIAE Phase 3 Clinical Trial in China**  
[https://www.nicox.com/assets/files/EN\\_OcumensionZerviateChinaPhase3Trial\\_20201230\\_P\\_R.pdf](https://www.nicox.com/assets/files/EN_OcumensionZerviateChinaPhase3Trial_20201230_P_R.pdf)
- January 5, 2021 **Nicox Highlights Successful 2020 Development Progress and Clinical Milestones for 2021**  
[https://www.nicox.com/assets/files/EN\\_Update-PR\\_20200105\\_F.pdf](https://www.nicox.com/assets/files/EN_Update-PR_20200105_F.pdf)
- January 6, 2021 **Nicox's Licensee Bausch + Lomb Launches VYZULTA® in Mexico**  
[https://www.nicox.com/assets/files/EN\\_VYZULTA-Launch-Mexico-PR\\_20210206\\_F.pdf](https://www.nicox.com/assets/files/EN_VYZULTA-Launch-Mexico-PR_20210206_F.pdf)
- January 20, 2021 **Nicox Provides Fourth Quarter 2020 Business Update and Financial Highlights**  
[https://www.nicox.com/assets/files/EN\\_Q4-2020-Results-PR\\_20210120\\_F1.pdf](https://www.nicox.com/assets/files/EN_Q4-2020-Results-PR_20210120_F1.pdf)
- January 22, 2021 **Nicox Analyst Coverage Initiated by Edison Investment Research**  
[https://www.nicox.com/assets/files/EN\\_Edison-Nicox-Initiation-PR\\_20210122\\_F1.pdf](https://www.nicox.com/assets/files/EN_Edison-Nicox-Initiation-PR_20210122_F1.pdf)
- January 29, 2021 **Nicox Amends Bond Financing Agreement with Kreos to Provide Financial Flexibility in 2021**  
[https://www.nicox.com/assets/files/EN\\_Kreos-Amendment-PR\\_20210129\\_F.pdf](https://www.nicox.com/assets/files/EN_Kreos-Amendment-PR_20210129_F.pdf)
- February 9, 2021 **BAUSCH HEALTH ANNOUNCES VYZULTA® (LATANOPROSTENE BUNOD OPHTHALMIC SOLUTION), 0.024%, IS NOW APPROVED IN SOUTH KOREA**  
[https://www.nicox.com/assets/files/EN\\_-Joint-PR\\_VYZULTA-approval-South-Korea\\_20210209\\_-F2.pdf](https://www.nicox.com/assets/files/EN_-Joint-PR_VYZULTA-approval-South-Korea_20210209_-F2.pdf)
- February 15, 2021 **Nicox's U.S. Licensee Eyevance Expands U.S. Promotion of ZERVIAE® In Agreement with Hikma**  
[https://www.nicox.com/assets/files/EN\\_ZERVIAEEyevanceNonOphthaCoPromote\\_PR\\_20210215\\_F.pdf](https://www.nicox.com/assets/files/EN_ZERVIAEEyevanceNonOphthaCoPromote_PR_20210215_F.pdf)
- February 23, 2021 **Nicox Announces the Publication in Leading Scientific Journal of Pre-Clinical Efficacy Results on a New Class of Non-PGA NO-donating IOP-Lowering Compounds**  
[https://www.nicox.com/assets/files/EN\\_NCX1741-JOPT-PR\\_20210223\\_F.pdf](https://www.nicox.com/assets/files/EN_NCX1741-JOPT-PR_20210223_F.pdf)



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**5.5 Competition**

**5.5.1 Overview**

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. We believe that our proprietary NO-donating research platform, knowledge, experience and scientific resources provide us with competitive advantages. However, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and governmental agencies and public and private research institutions. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future.

Our potential competitors include large pharmaceutical and biotechnology companies, and specialty pharmaceutical and generic drug companies. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization. Many of our potential competitors have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient recruitment for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

The key competitive factors affecting the success of each of our product candidates, if approved for marketing, are likely to be its efficacy, safety, method of administration, convenience, price, the level of generic competition and the availability of coverage and adequate reimbursement from government and other third-party payors.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third party payors seeking to encourage the use of generic products.

Our product candidates target markets that are already served by a variety of competing products based on a number of active pharmaceutical ingredients. Many of these existing products have achieved widespread acceptance among physicians, patients and payors for the treatment of ophthalmic diseases and conditions. In addition, many of these products are available on a generic basis, and our product candidates may not demonstrate sufficient additional clinical benefits to physicians, patients or payors to justify a higher price compared to generic products. In many cases, insurers or other third-party payors, particularly Medicare, seek to encourage the use of generic products. Given that we are developing products based on FDA approved therapeutic agents, our product candidates, if approved, will face competition from generic and branded versions of existing drugs based on the same active pharmaceutical ingredients that are administered in a different manner, such as biodegradable drug product formulations.

Because the active pharmaceutical ingredients in some of our product candidates are available on a generic basis, or are soon to be available on a generic basis, competitors may be able to offer and sell products with the same active pharmaceutical ingredient as our products so long as these competitors do not infringe our patents. For example, our patents covering our NO-donating compounds largely claim new composition of matter. However, intellectual property covering certain other products such as ZERVATE and NCX 4251 relate to the formulation and method of use of these compounds. As such, if a third party were able to design around the formulation and process patents that we hold and to create a different formulation using a different production



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process not covered by our patents or patent applications, we would likely be unable to prevent that third party from manufacturing and marketing its product.

### 5.5.2 Reduction of IOP in patients with glaucoma and ocular hypertension

Prostaglandin analogs are used as first line IOP lowering therapy and account for more than 50% of prescriptions for IOP lowering drugs in the U.S., where the leading branded product by sales is LUMIGAN (bimatoprost ophthalmic solution) 0.03% from Allergan, the other leading branded product is TRAVATAN Z (travoprost ophthalmic solution) 0.004% from Novartis, and the leading generic product is latanoprost. Rocklatan (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%, a fixed dose combination of netarsudil and latanoprost, was also approved and launched in the U.S. by Aerie Pharmaceuticals, or Aerie, in 2019. It was also approved in Europe in January 2021, under the brand name Roclanda. XELPROS (latanoprost ophthalmic emulsion) 0.005% was recently approved for IOP lowering in patients with open-angle glaucoma or ocular hypertension and was launched in the U.S. by a subsidiary of Sun Pharmaceutical Industries Ltd in 2019. Allergan, Inc., an Abbvie company, launched Durysta, a bimatoprost extended release biodegradable for IOP lowering, in the U.S. in 2020. The other products in the market, currently used mostly as adjunct therapies added on the top of PGAs, are alpha agonists, beta blockers and carbonic anhydrase inhibitors, most of which are available as generic as well as branded forms. Another adjunct therapy, Rhopressa (netarsudil ophthalmic solution) 0.02%, a Rho kinase inhibitor, was approved and launched in the U.S. by Aerie in 2018, and was approved under the brand name Rhokiinsa in Europe in 2019.

Several competitors are developing new formulations, novel chemical compounds and other sustained drug release products for the same ophthalmic indications as our current NO-donating compounds for IOP lowering. The list below sets out the principal programs in Phase 3 (excluding generics of existing, approved products):

- *Glaukos* is conducting Phase 3 clinical development of the iDose insert or implant, which is a non-biodegradable metal insert that secretes travoprost and is placed in the eye during a surgical procedure.
- *Laboratorios Sophia S.A.de C.V.* is conducting Phase 3 clinical development of PRO-067, a cyclodextrin containing formulation of latanoprost that is aimed at improving the stability of currently available latanoprost formulations.
- *Ocular Therapeutix, Inc.* has conducted Phase 3 clinical development of OTX-TP, a sustained release travoprost punctal plug formulation that is aimed at lowering IOP, which did not meet its primary endpoint. Other clinical studies are ongoing.
- *Santen* is developing DE117, an EP2 agonist for the lowering of IOP. It has been launched in Japan under the brand name EYBELIS and an NDA filing in the U.S. was planned for 2020.

### 5.5.3 Competitors to our other pipeline product candidates

We may also be exposed to potentially competitive products which may be under development for our other indications.

#### *Allergic conjunctivitis*

The allergic conjunctivitis market is dominated by Alcon Laboratories, Inc.'s PAZEO, PATANOL and PATADAY, three products based on olopatadine at different concentrations, together with generic olopatadine products. Olopatadine is now also available as a non-prescription drug in the U.S. The list below sets out the principal programs in Phase 3 (excluding generics of existing, approved products):

- *Aldeyra Therapeutics, Inc.*, is in Phase 3 clinical trials with reproxalap (ADX102) for allergic conjunctivitis.



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- *Faes Pharma*, has completed a Phase 3 clinical trial in the U.S. with bilastine for allergic conjunctivitis.
- *Ocular Therapeutix, Inc.* is developing Dextenza, a dexamethasone insert. It has completed a Phase 3 clinical trial for allergic conjunctivitis and an NDA submission was made in December 2020.

### *Blepharitis*

There is currently no treatment approved solely for blepharitis, although certain drugs, notably steroids, are known to be used off-label for steroid-responsive inflammation of the palpebral (eyelid) conjunctiva. There are also antibiotic and antimicrobial products, such as ointments and eye drops, indicated for the treatment of blepharitis, along with other conditions. The list below sets out the principal programs in Phase 3 (excluding generics of existing, approved products):

- *Sun Pharma* is developing ISV-305, dexamethasone in DuraSite® 2, targeting the treatment of blepharitis, which has completed a Phase 3 clinical trial.
- *Tarsus Pharmaceuticals* is developing TP-03 for demodex blepharitis, currently in a Phase 2b/3 clinical trial.

### 5.5.4 Other NO-delivery and NO-donating technologies

As far as we are aware, there are at least eight pharmaceutical companies working in the field of NO-donating drugs:

- *AntiRadical Technologies* is developing caged NO molecules for the treatment of life threatening disruption of blood flow.
- *Bellerophon Therapeutics, Inc.* is currently developing the INOpulse, an NO device system product in the U.S. for the treatment of various conditions related to pulmonary hypertension.
- *Edixomed* is developing *in-situ* generation of NO for application in wound care, dermatology, critical care, respiratory and transdermal drug delivery
- *Kowa Pharmaceutical Europe Co. Ltd.* markets HYPADIL Kowa Ophthalmic Solution 0.25% in Japan for the treatment of glaucoma and intraocular hypertension. The active ingredient of this drug is nipradilol, an alpha- and beta-adrenergic blocker with NO-releasing action.
- *Mallinckrodt PLC* markets INOmax in the United States, a gaseous NO product for the treatment of persistent pulmonary hypertension of the newborn.
- *Novan Therapeutics* is developing NO donors for the treatment of acne, viral infections, onychomycosis and inflammatory skin disease. Their most advanced program is in Phase 3.
- *Topadur* is developing an NO-releasing PDE5 inhibitor to accelerate chronic wound closure.
- *Vast Therapeutics* is developing controlled and local delivery of NO via macromolecules for treatment of severe respiratory infections in patients with cystic fibrosis.
- *Zylo Therapeutics* is developing transdermal drug delivery systems including NO.

It is important to note that once marketed (subject to obtaining marketing approvals on an ad-hoc basis), the products developed by us will be competing with a number of products that are already commercially available. In addition, research conducted by the pharmaceutical industry and by public and private institutions will continue to generate new products that could compete with our existing or future commercial products.

## Press Release

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# Nicox Announces 2020 Financial Results and 2021 Key Milestones

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- **Net revenue<sup>1</sup> of €12.9 million in 2020 almost doubled versus 2019**
- **Cash position increased to €47.2 million as of December 31, 2020**

March 1<sup>st</sup>, 2021 – release at 7:30 am CET  
Sophia Antipolis, France

**Nicox SA** (Euronext Paris: FR0013018124, COX), an international ophthalmology company, today announced the financial and operating results for Nicox and its subsidiaries (the “Nicox Group”) for the year ended December 31, 2020, as approved by the Board of Directors on February 26, 2021, and provided upcoming 2021 key milestones.

### 2020 Financial Summary

Net revenue<sup>1</sup> for the full year 2020 was €12.9 million (€2.4 million in net royalties, €10.5 million in license payments), compared to €6.9 million (€2.1 million in net royalties, €4.8 million in upfront and milestone payments) for the full year 2019. Net revenue has been revised upwards from that reported in the Q4 2020 business update due to an accounting adjustment reflecting a non-cash item of deferred income received from Ocumension in March 2020.

Operating expenses for the year 2020 decreased to €19.5 million from €25.5 million for the 12 months to December 31, 2019. Research and development expenses decreased by €5.0 million while administrative and other expenses decreased by €1.0 million. Nicox’s research and development efforts remained strong in 2020, mainly concentrated in the second part of the year with 3 clinical trials initiated since June.

Net loss of the Nicox Group for the full year 2020 was €18.1 million against €18.9 million for the full year 2019.

As of December 31, 2020, the Nicox Group had cash and cash equivalents of €47.2 million as compared with €28.1 million at December 31, 2019.

As of December 31, 2020, the Nicox Group had financial debt of €17.9 million consisting of €15.9 million in the form of a bond financing agreement with Kreos Capital signed in January 2019 and a €2.0 million credit agreement with Société Générale and LCL, guaranteed by the French State, and granted in August 2020 in the context of the COVID-19 pandemic. The position includes the prepayment to Kreos of the January 2021 period.

### Events after the Reporting Period

- VYZULTA® (latanoprostene bunod ophthalmic solution), 0.024%, was launched by Nicox’s global partner Bausch + Lomb in Mexico. It is already commercialized in U.S. (2017), Canada (2019), Argentina (2020) and Hong Kong (2020), and approved in 4 other territories, Colombia, South Korea, Taiwan and Ukraine. Bausch + Lomb is planning to launch VYZULTA in Taiwan in 2021 and in South Korea in 2022.
- Nicox amended its bond financing agreement with Kreos Capital, introducing an additional one-year period of interest-only payments on the outstanding principal starting on February 1, 2021, and an

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<sup>1</sup> Net revenue consists of revenue from collaborations less royalty payments which corresponds to Net profit in the consolidated statements of profit or loss



extension of the overall period of the loan by 6 months to July 2024. The new one-year interest-only period is expected to provide approximately €5.5 million of additional flexibility for investment in development activities in 2021. The interest rate of the bonds remains unchanged as a result of this amendment.

- Pre-clinical intraocular pressure (IOP)-lowering results on a new class of non-prostaglandin analog, nitric oxide (NO)-donating compounds, was published in the *Journal of Ocular Pharmacology and Therapeutics*, a leading scientific journal. Increased IOP is one of the principal risk factors of open-angle glaucoma. The NO-mediated IOP-lowering effect in this new class of compounds is enhanced by concomitant action of phosphodiesterase type-5 inhibition within the same molecule.

### Key Expected Upcoming Milestones

- **NCX 470 first Phase 3 clinical trial, Mont Blanc:** Nicox's lead clinical product candidate, NCX 470 is a novel NO-donating prostaglandin analog. Mont Blanc is a 3-month trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1%, against latanoprost ophthalmic solution, 0.005%, for lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Top-line results are currently expected in H1 2022.
- **NCX 4251 Phase 2b clinical trial, Mississippi:** NCX 4251 is a novel patented ophthalmic suspension of fluticasone propionate nanocrystals. Mississippi is evaluating once-daily dosing NCX 4251 0.1% versus placebo for the treatment of acute exacerbations of blepharitis. Top-line results are currently expected in Q4 2021.
- We expect to enter into additional agreements for **ZERVIAE®** (cetirizine ophthalmic solution), 0.24%, further enlarging the licensed territories and increasing potential future revenue.

*We continue to closely watch the spread and impact of the COVID-19 pandemic and we will provide an update of any delays.*

### About Nicox

Nicox S.A. is an international ophthalmology company developing innovative solutions to help maintain vision and improve ocular health. Nicox's lead program in clinical development is NCX 470, a novel nitric oxide-donating prostaglandin analog, for lowering intraocular pressure in patients with glaucoma. The company is also developing NCX 4251, a proprietary formulation of fluticasone, for acute exacerbations of blepharitis. Nicox generates revenue from VYZULTA® in glaucoma, licensed exclusively worldwide to Bausch + Lomb, and ZERVIAE® in allergic conjunctivitis, licensed in multiple geographies, including to EyeVance Pharmaceuticals, LLC, in the U.S. and Ocumension Therapeutics in the Chinese and in the majority of South East Asian markets.

Nicox is headquartered in Sophia Antipolis, France, is listed on Euronext Paris (Compartment B: Mid Caps; Ticker symbol: COX) and is part of the CAC Healthcare, CAC Pharma & Bio and Next 150 indexes.

For more information on Nicox, its products or pipeline, please visit: [www.nicox.com](http://www.nicox.com).

### Analyst coverage

Bryan, Garnier & Co	Victor Floc'h	Paris, France
Cantor Fitzgerald	Louise Chen	New York, U.S.
Edison Investment Research	Pooya Hemami	London, UK
H.C. Wainwright & Co	Yi Chen	New York, U.S.
Kepler Cheuvreux	Damien Choplain	Paris, France



*The views expressed by analysts in their coverage of Nicox are those of the author and do not reflect the views of Nicox. Additionally, the information contained in their reports may not be correct or current. Nicox disavows any obligation to correct or to update the information contained in analyst reports.*

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### Forward-Looking Statements

The information contained in this document may be modified without prior notice. This information includes forward-looking statements. Such forward-looking statements are not guarantees of future performance. These statements are based on current expectations or beliefs of the management of Nicox S.A. and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. Nicox S.A. and its affiliates, directors, officers, employees, advisers or agents, do not undertake, nor do they have any obligation, to provide updates or to revise any forward-looking statements.

Risks factors which are likely to have a material effect on Nicox's business are presented in the 3<sup>rd</sup> chapter of the '*Document d'enregistrement universel, rapport financier annuel et rapport de gestion 2019*' filed with the French *Autorité des Marchés Financiers* (AMF) on March 6, 2020 which are available on Nicox's website ([www.nicox.com](http://www.nicox.com)) and as restated in the 4<sup>th</sup> chapter of the half yearly financial report as of June 30, 2020, which is also available on Nicox's website.

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## CONSOLIDATED STATEMENTS OF PROFIT OR LOSS

	As of December 31:	
	2020	2019
Revenue from collaborations	14,423	8,260
Royalty payments	(1,516)	(1,405)
<b>Net profit</b>	<b>12,907</b>	<b>6,855</b>
Research and development expenditures	(12,728)	(17,747)
Administrative expenses	(6,677)	(7,666)
Other income	1,083	970
Other expenses	(93)	(85)
<b>Operating loss before amortization of intangible assets</b>	<b>(5,508)</b>	<b>(17,673)</b>
Amortization of intangible assets	(1,252)	(659)
<b>Operating loss</b>	<b>(6 760)</b>	<b>(18,332)</b>
Finance income	1,168	2,565
Finance expense (1)	(12,478)	(7,013)
<b>Net financial income, (expense)</b>	<b>(11,310)</b>	<b>(4,446)</b>
<b>Loss before tax</b>	<b>(18,070)</b>	<b>(22,778)</b>
Income tax (expense) / benefit (2)	(28)	3,856
<b>Loss after tax</b>	<b>(18,098)</b>	<b>(18,922)</b>
<b>Loss for the period</b>	<b>(18,098)</b>	<b>(18,922)</b>

<sup>(1)</sup> Finance expense in 2020 included a net loss of € (6.9) million following the divestment of the VISUfarma shareholding, € (2.2) million of loan interests paid to Kreos and € (3.4) million of foreign exchange loss. In 2019 Finance expenses included an impairment of € (6.1) million related to VISUfarma shareholding and (0.8) million of loan interests paid to Kreos.

<sup>(2)</sup> Income tax (expense) / benefit in 2019 included a non-cash item of €3.7 million for the first recognition of deferred tax assets related to ZERVIAE

## CONSOLIDATED STATEMENTS OF FINANCIAL POSITION

	As of December 31:	
	2020	2019
<b>ASSETS</b>		
<b>Non-current assets</b>		
Goodwill	23,663	25,847
Intangible assets	64,848	72,120
Property, plant and equipment	1,166	1,670
Non-Current financial assets (1)	68	11,023
<b>Total non-current assets</b>	<b>89,745</b>	<b>110,660</b>
<b>Current assets</b>		
Trade receivables	1,723	1,069
Government grants receivables	736	864
Other current assets	237	1,297
Prepayments	2,630	814
Cash and cash equivalents	47,195	28,102
<b>Total current assets</b>	<b>52,521</b>	<b>32,146</b>
<b>TOTAL ASSETS</b>	<b>142,266</b>	<b>142,806</b>
<b>EQUITY AND LIABILITIES</b>		
<b>Shareholders' equity</b>		
Issued capital	37,030	33,231
Share premium	528,595	518,441
Cumulative translation adjustment	2,959	7,811
Treasury Shares	(605)	-
Accumulated deficit	(467,169)	(450,186)
<b>Total equity</b>	<b>100,810</b>	<b>109,297</b>
<b>Non-current liabilities</b>		
Non-current financial liabilities	13,429	10,168
Deferred taxes liabilities	11,868	12,964
Provisions	754	549
<b>Total non-current liabilities</b>	<b>26,051</b>	<b>23,681</b>
<b>Current liabilities</b>		
Current financial liabilities	5,646	2,481
Trade payables	2,422	4,996
Deferred income	5,174	-
Other current liabilities	2,163	2,351
<b>Total current liabilities</b>	<b>15,405</b>	<b>9,828</b>
<b>TOTAL LIABILITIES AND EQUITY</b>	<b>142,266</b>	<b>142,806</b>

(1) Divestment of VISUfarma shareholding and loan notes in 2020

## Press Release

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# Nicox's NCX 470 Receives Approval by Chinese Authorities for Local Start of Denali Phase 3 Trial

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March 4, 2021 – release at 7:30 am CET  
Sophia Antipolis, France

**Nicox SA** (Euronext Paris: FR0013018124, COX), an international ophthalmology company, today announced that its partner, Ocumension Therapeutics, has received approval from China's Center for Drug Evaluation of the National Medical Products Administration to conduct the Chinese part of the ongoing NCX 470 Denali Phase 3 clinical trial for the lowering of intraocular pressure (IOP) in patients with open angle glaucoma or ocular hypertension.

Nicox's lead clinical product candidate, NCX 470, is a novel nitric oxide (NO)-donating prostaglandin analog licensed exclusively to Ocumension Therapeutics for the Chinese, Korean and South East Asian markets.

**Dr. José Boyer, Interim Head of R&D at Nicox**, said: *"This approval allows us to initiate Chinese patients in the Denali trial on schedule. This will pave the way for Nicox and Ocumension to submit New Drug Applications in parallel in the U.S. and China, respectively, and potentially bring NCX 470 to these two important markets in similar timeframes."*

The Press Release by Ocumension can be found [here](#).

**Denali, the second Phase 3 trial of NCX 470** for the lowering of IOP in patients with open-angle glaucoma or ocular hypertension, was initiated in the U.S. on November 9, 2020. Denali is a 3-month trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1% versus latanoprost ophthalmic solution, 0.005% and will also include a long-term safety extension. The trial is financed jointly and in equal parts by Nicox and Ocumension and includes clinical sites in both the U.S. and China, with the majority of the patients to be recruited in the U.S. The Denali trial, together with the ongoing Mont Blanc trial, are designed to fulfill the regulatory requirements for Phase 3 safety and efficacy trials to support New Drug Application (NDA) submissions in the U.S. and China. Top-line results are currently expected in Q4 2022.

NCX 470 is also being studied in Mont Blanc, a 3-month trial evaluating the safety and efficacy of NCX 470 ophthalmic solution, 0.1%, against latanoprost ophthalmic solution, 0.005%, for lowering of IOP in patients with open-angle glaucoma or ocular hypertension. Top-line results are currently expected in H1 2022.

### About NCX 470

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NCX 470 is a novel, potential best-in-class, nitric oxide (NO)-donating prostaglandin analog in development to reduce intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension. Glaucoma is a group of ocular diseases in which the optic nerve is injured, leading to peripheral and, ultimately, central visual field loss and it can eventually lead to blindness if not treated. It is frequently linked to abnormally high IOP (~90% of patients) due to blockage or malfunction of the eye's aqueous humor drainage system in the front of the eye. In 2019, worldwide sales of treatments targeting glaucoma were over \$6.0 billion out of a \$21.9 billion worldwide market for ophthalmic drugs.

NCX 470 is designed to release both bimatoprost and NO following instillation into the eye. Bimatoprost, marketed under the brand name LUMIGAN® by Allergan, Inc., is one of the leading products in the class of prostaglandin analogs, the most widely used class of drugs for IOP-lowering in patients with open-angle glaucoma or ocular hypertension.

### About Nicox

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Nicox S.A. is an international ophthalmology company developing innovative solutions to help maintain vision and improve ocular health. Nicox's lead program in clinical development is NCX 470, a novel nitric oxide-donating prostaglandin analog, for lowering intraocular pressure in patients with glaucoma. The company is also developing NCX 4251, a proprietary formulation of fluticasone, for acute exacerbations of blepharitis. Nicox generates revenue from VYZULTA® in glaucoma, licensed exclusively worldwide to Bausch + Lomb, and ZERVIA® in allergic conjunctivitis, licensed in multiple geographies, including to Eyevance Pharmaceuticals, LLC, in the U.S. and Ocumension Therapeutics in the Chinese and in the majority of South East Asian markets.

Nicox is headquartered in Sophia Antipolis, France, is listed on Euronext Paris (Compartment B: Mid Caps; Ticker symbol: COX) and is part of the CAC Healthcare, CAC Pharma & Bio and Next 150 indexes.

For more information on Nicox, its products or pipeline, please visit: [www.nicox.com](http://www.nicox.com).

### Analyst coverage

Bryan, Garnier & Co	Victor Floc'h	Paris, France
Cantor Fitzgerald	Louise Chen	New York, U.S.
Edison Investment Research	Pooya Hemami	London, UK
H.C. Wainwright & Co	Yi Chen	New York, U.S.
Kepler Cheuvreux	Damien Choplain	Paris, France



*The views expressed by analysts in their coverage of Nicox are those of the author and do not reflect the views of Nicox. Additionally, the information contained in their reports may not be correct or current. Nicox disavows any obligation to correct or to update the information contained in analyst reports.*

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### Forward-Looking Statements

The information contained in this document may be modified without prior notice. This information includes forward-looking statements. Such forward-looking statements are not guarantees of future performance. These statements are based on current expectations or beliefs of the management of Nicox S.A. and are subject to a number of factors and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. Nicox S.A. and its affiliates, directors, officers, employees, advisers or agents, do not undertake, nor do they have any obligation, to provide updates or to revise any forward-looking statements.

Risks factors which are likely to have a material effect on Nicox's business are presented in the 3<sup>rd</sup> chapter of the 'Document d'enregistrement universel, rapport financier annuel et rapport de gestion 2020' filed with the French Autorité des Marchés Financiers (AMF) on March 1, 2021 which are available on Nicox's website ([www.nicox.com](http://www.nicox.com)).

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# REQUEST FOR DOCUMENTS

Ordinary and Extraordinary Shareholder Meetings of April 14, 2021.

I,  
LAST Name : .....

First Name: .....

Address :  
.....

Email: .....

Owner of ..... registered shares\*

And/ or ..... bearer shares,

Of **NICOX SA**

Hereby acknowledge that I have received the documents pertaining to the aforementioned General Meetings pursuant to article R.225-81 of the Code de Commerce.

request that the documents and information pertaining to the General Shareholder Meetings of April 14, 2021, as provided for under article R.225-83 of the same Code be addressed to my attention.

Signed in ....., on ..... 2021

Signature

\* Pursuant to article R.225-88 paragraph 3 of the Code de Commerce, holders of registered shares may submit a request to the company for a copy of all documents and information stipulated in article R.225-81 and R.225-83 of the Code de Commerce for each subsequent general meeting. The shareholder must mention her/his desire to exercise this right in the present request.