BioHAnce™

ACIDE HYALURONIQUE (AH)
RÉTICULÉ

DÔMES
PHARMA

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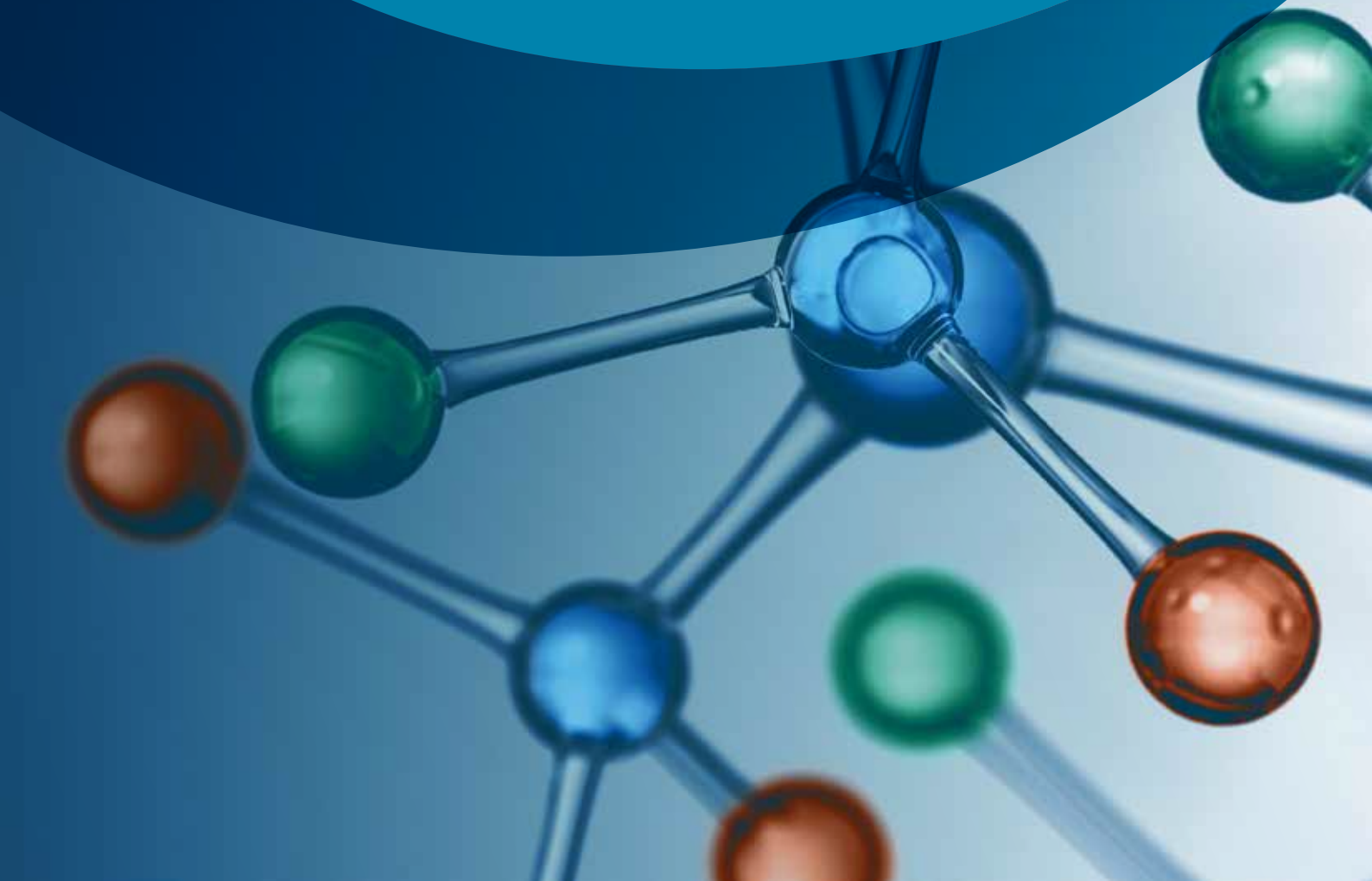
1

BioHAnce™

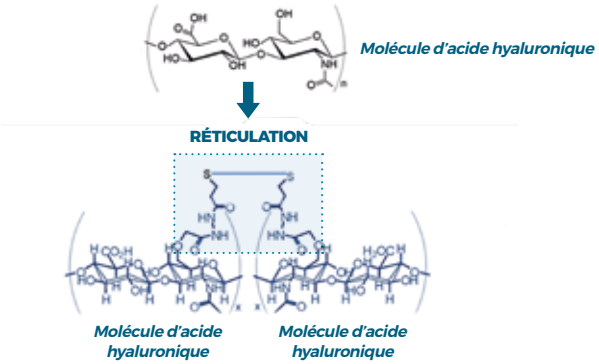
LA TECHNOLOGIE



1 L'ACIDE HYALURONIQUE RÉTICULÉ (AH) BIOHANCE™

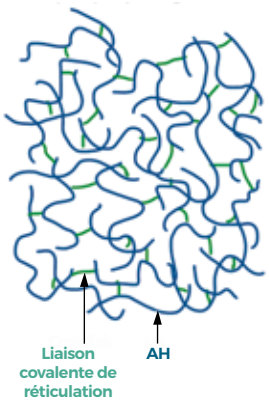
Une technologie brevetée

BioHAnce™ est une technologie brevetée qui utilise un procédé en bio-ingénierie innovant afin de créer une matrice moléculaire d'acide hyaluronique (AH) réticulé. **Cet échafaudage moléculaire possède des propriétés physiques et chimiques uniques, permettant d'améliorer l'hydratation des tissus, d'accélérer le processus de cicatrisation et de prolonger l'adhérence à la surface oculaire.**



Les propriétés de l'acide hyaluronique réticulé BioHAnce™

L'AH est une substance physiologiquement présente dans le corps humain y compris chez les animaux. Cette molécule joue un rôle primordial dans l'hydratation et la lubrification de nombreux tissus ainsi que dans le processus de cicatrisation. Cet AH se dégrade rapidement limitant ses applications cliniques et son efficacité. Grâce à la technologie BioHAnce™ brevetée, l'AH est modifié chimiquement **le rendant ainsi plus résistant à la dégradation enzymatique, tout en garantissant un environnement optimal pour améliorer les processus naturels de cicatrisation. Grâce à ses propriétés muco-adhésives uniques, l'hydratation et la lubrification des tissus sont prolongées.** La concentration en AH BioHAnce™ varie en fonction de l'utilisation recherchée.



Hydrogel d'AH réticulé

La technologie BioHAnce™ permet la création d'une matrice moléculaire réticulée qui améliore le processus de cicatrisation naturelle

Comment comparer notre AH réticulé aux autres AH réticulés disponibles sur le marché ?

Notre AH réticulé BioHAnce™ est **un produit purifié qui ne contient aucun composé ou sous-produit toxique pouvant avoir un effet nocif ou irritant.** En revanche, les processus de réticulation traditionnellement utilisés peuvent induire une faible biocompatibilité, déclencher une réponse immunitaire accrue, ou engendrer de l'inflammation.

Une plateforme technologique

Notre polymère fonctionnel (molécule créée par l'assemblage de plusieurs petits monomères), obtenu chimiquement par cette technologie, **peut être réticulé avec d'autres molécules.** Non seulement la technologie BioHAnce™ peut être employée seule mais elle permet également d'agir comme une technologie de support. Nous souhaitons, **à l'avenir, exploiter pleinement ce potentiel en y incorporant des substances actives** afin d'en faire un « véhicule » de la substance active.

2 EN QUOI CONSISTE NOTRE TECHNOLOGIE

BioHAnce™ est créé en effectuant deux modifications sur l'acide hyaluronique. Nous avons recours à un acide hyaluronique de qualité médicale, issu d'un processus de fermentation bactérienne, sans produit d'origine animale. Cet AH est modifié et purifié avant toute incorporation dans nos solutions oculaires. Après une étape finale de purification, la solution est filtrée de façon stérile puis est réticulée de manière aseptique formant ainsi notre produit fini : un gel d'AH.

3 PRINCIPAUX AVANTAGES DE L'AH RÉTICULÉ BIOHANCE™

- Améliore l'hydratation, la lubrification, le confort oculaire et aide à stabiliser le film lacrymal.[1]
- Augmente le temps de rémanence (versus l'AH linéaire) : il persiste 2 à 5 fois plus longtemps que les larmes artificielles traditionnelles.[2,3]
- Nécessite un nombre d'applications moindre (BID), ce qui améliore l'observance d'un traitement.
- Forme une fine barrière apaisante et protectrice de l'œil, sans altérer la vision.
- L'AH réticulé Biohance ™ concentré à 0.75% permet une reconstruction plus rapide de la cornée (par rapport à l'AH linéaire) : jusqu'à 34%[4]
- Prolonge la présence des traitements topiques sur la surface oculaire[5]
- Ne se lie pas aux antibiotiques (contrairement au sérum autologue)[7]
- La technologie BioHAnce™ a été créée spécifiquement pour la santé animale
- Très bonne tolérance :
  - Sans conservateurs
  - La réticulation au thiol permet l'obtention d'un produit final purifié (sans résidu réticulé pouvant être irritant pour l'œil ou générer de l'inflammation)

4 EVITER LA FORMATION D'« AMAS » COLLANT

Comparaison de l'AH réticulé et de l'AH non-réticulé (linéaire)

Produit A

Amas collant sur l'œil de l'animal

Remend® 0.4

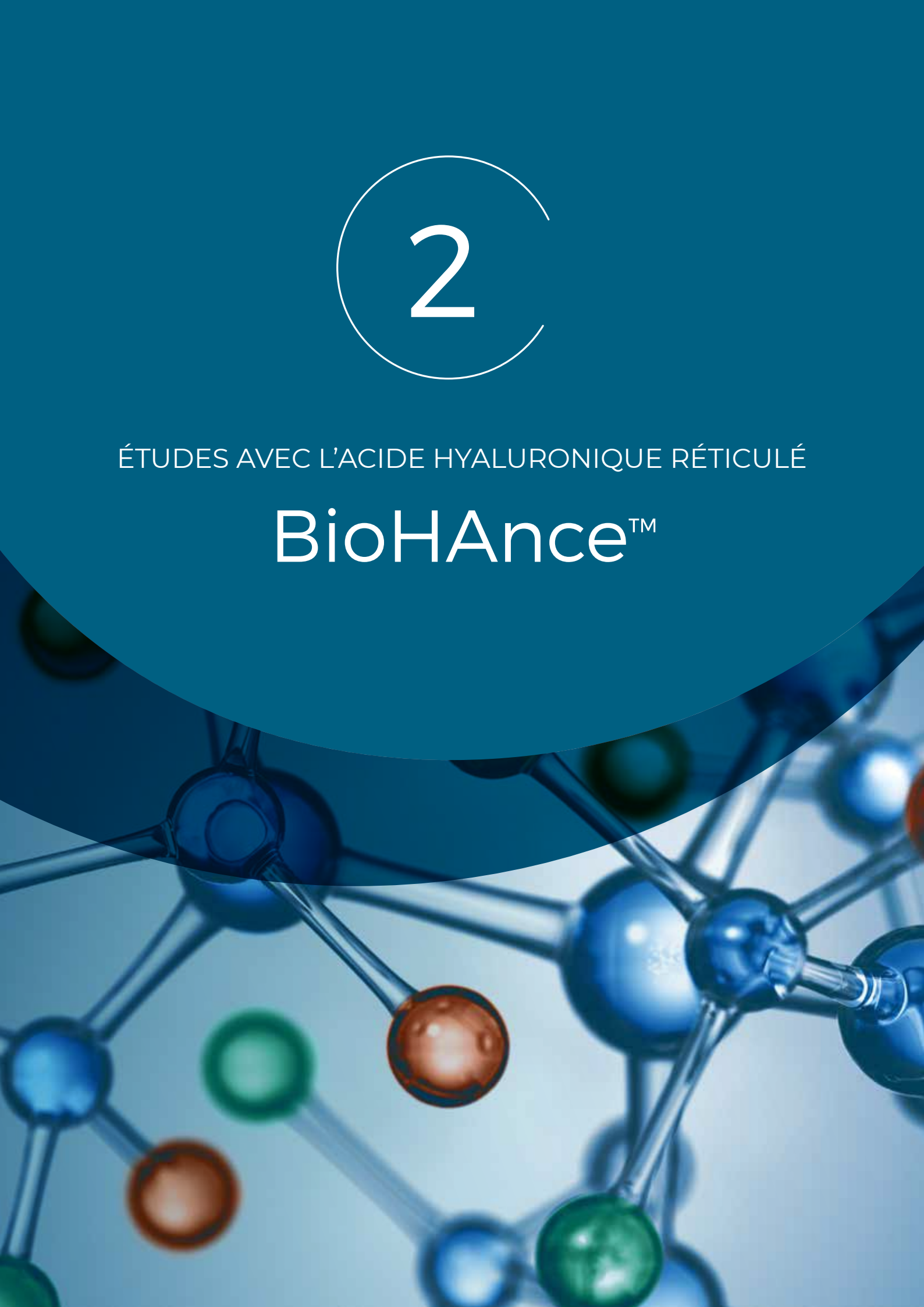
Goutte de gel transparente qui étale un film transparent et fin sur toute la surface de l'œil après chaque clignement palpébral

- **Le phénomène de réticulation forme un gel lubrifiant, de consistance plus visqueuse et cela, à une concentration plus faible.** De plus, la réticulation procure des propriétés muco-adhésives qu'une molécule d'AH linéaire ne possède pas. Par conséquent, cela permet à la molécule d'AH réticulé de rester plus longtemps à la surface oculaire et donc de limiter son élimination lors des clignements des paupières contrairement aux gouttes oculaires traditionnelles, contenant de l'AH non réticulé.
- **Après sa transformation en forme réticulée, les propriétés chimiques et physiques de l'AH sont modifiées.** C'est pour cette raison qu'il est impossible de comparer les concentrations en AH entre un produit à base d'AH linéaire et un produit à base d'AH réticulé. Le processus de réticulation va effectivement former un AH de poids moléculaire extrêmement élevé, qui possèdera des propriétés physiques différentes.
- Plus le poids moléculaire d'un produit est important, plus il est difficile de l'incorporer dans une solution. **Néanmoins, grâce à notre technologie brevetée, nous pouvons presque nous en affranchir et ainsi réaliser à grande échelle toutes les étapes de purifications et filtrations stérilisantes.**

2

ÉTUDES AVEC L'ACIDE HYALURONIQUE RÉTICULÉ

BioHAnce™



1

EVALUATION OF TOPICALLY APPLIED CROSS-LINKED HYALURONIC ACID (REMEND®) ON THE OCULAR SURFACE OF CLINICALLY HEALTHY DOGS[1]

ACVO 2022 POSTER SESSION - SUBMITTED FOR PUBLICATION

L'application topique de l'AH réticulé BioHAnce™ (Remend® 0,4) peut améliorer la qualité des larmes, notamment en stabilisant le film lacrymal chez les chiens.

(CE Plummer[1], BC Martins[2], C Bolch[3], PS Martinez[1], Carbia BE[1])
1: College of Veterinary Medicine, University of Florida; 2: School of Veterinary Medicine, University of California Davis; 3: Institute for Vision Research, University of Florida

Purpose

To evaluate effects of a topically applied cross-linked HA (Remend Eye Lubricating Drops® - Bayer Animal Health) on the ocular surface of clinically normal dogs.

Methods

Twenty dogs with normal ophthalmic examinations received tear ferning tests (TF-M7, TF-M5, and TF-R), Schirmer's tear test (STT-I), tear film breakup time (TFBUT), slit-lamp biomicroscopy , indirect ophthalmoscopy and rose Bengal dye staining (RB) on the first day of examination (day 0), 1 week after initial examination (day 7), and 2 weeks after examination (day 14). Following examination and baseline testing, subjects received cross-linked HA (Remend®) two times a day (BID) on the right eye (OD). The left eye (OS) served as control and received saline BID. Tear fluid samples from both treated and control eyes were evaluated for HA levels by ELISA prior to end at several time points following treatment.

Results

For the duration of the study, there was no statistically significant difference in aqueous tear production (STT-I) or RB retention between study and control eyes. There was a statistically significant improvement in TFBUT between study and control eyes on Day 7 ($p<0.001$) and Day 14 ($p<0.001$). There was a statistically significant improvement in TF-M7 scores ($p<0.02112$) and TF-R scores by Day 14 ($p< 0.01097$). HA was present in measurable quantities in the tear fluid at 30 minutes and one hour after topical application in treated eyes.

CONCLUSIONS

Topically applied cross-linked HA may improve tear quality, especially tear film stability, in dogs.
Supported by Bayer Animal Health.

2

FLUOROMETRIC EVALUATION OF CROSS-LINKED VS LINEAR HYALURONIC ACID EYE LUBRICANTS[2]

ACVO 2022 POSTER SESSION - SUBMITTED FOR PUBLICATION

L'AH réticulé BioHAnce™ a démontré un recouvrement plus large de la surface oculaire et un temps de contact avec la surface oculaire significativement prolongé (jusqu'à 180 minutes) comparativement à l'AH linéaire (jusqu'à 36 minutes).

(F Montiani Ferreira[2], SK Atzet, AD Fankhauser[1], EK Behan[1], DJ Haeussler[3])
1: SentrX Animal Care; 2: Veterinary Medicine Department, Federal University of Paraná; 3: Animal Eye Institute

Purpose

This study evaluated the residence time of linear versus cross-linked hyaluronic acid (XHA) on the canine ocular surface, using covalently labeled fluorescent compound. This allows for evaluation of the actual presence of XHA, as opposed to the bulk medium (water).

Methods

Linear HA and XHA were covalently modified using AlexaFluor 488 reactive moities. Physical properties of the solutions were also evaluated for concentrations, viscosity and shear thinning profiles. Eye drops were applied to eyes of 18 dogs that were previously assessed and determined to have normal baseline ocular health (STT, slit-lamp biomicroscopy, tonometry and fundoscopy). Using a blue light filter (450-490 nm), digital images were obtained, from instillation to 180 minutes. Images were analyzed assessing the percent of the total ocular area covered with green fluorescence at various time points.

Results

All HA samples were successfully modified with approximately 5 mol% Alexa-Fluor. Viscosity varied from 0.4 to 32 Pa-s and all samples exhibited shear thinning . Linear HA quickly migrated to the tear meniscus and could be quantified up to 36 min. XHA exhibited a dual phase behavior: a wide surface coverage first, lasting up to 50 min, then accumulating in tear film meniscus and medial canthus in the second phase, remaining in contact with the ocular surface up to 180 min.

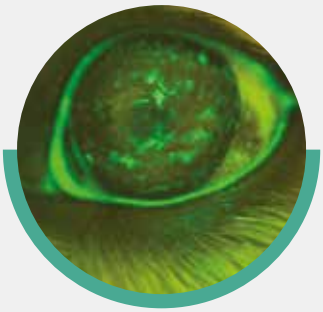
CONCLUSIONS

XHA exhibited a broader ocular surface coverage and a significantly increased ocular surface contact time compared with linear HA. Not only could this indicate extended lubrication but, potentially, could be used as a topical sustained-release drug application method.

Supported by SentrX Animal Care.

L'AH réticulé BioHAnce™ a manifesté un comportement en deux phases. Dans un premier temps, l'AH a démontré un recouvrement large de la surface oculaire qui a persisté jusqu'à 50min. Puis, dans un second temps, il s'est accumulé dans le ménisque lacrymal et dans le canthus médial, permettant ainsi un temps de contact avec la surface oculaire allant jusqu'à 180 minutes.

1ST PHASE Wide surface coverage



BioHAnce™ cross-linked HA (0.75%)
0 min

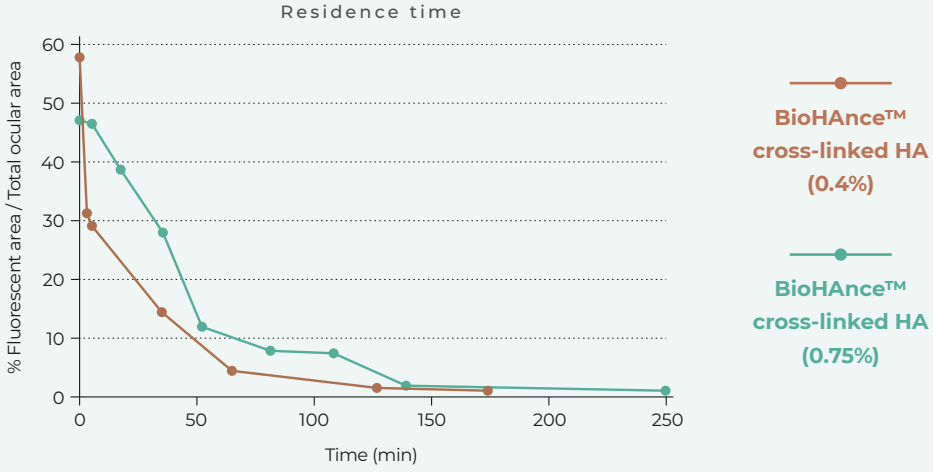
BioHAnce™ cross-linked HA (0.75%)
5 min

2ND PHASE Medial canthus deposit phase (slow release)

BioHAnce™ cross-linked HA (0.75%)
180 min

Everted eyelid showing deposit
BioHAnce™ cross-linked HA (0.75%)
180 min

Additional privately held study performed by SentrX Animal Care with healthy dog eyes



3 PROOF OF CONCEPT STUDY COMPARING HEALING RATES OF BIOHANCE™ CROSS-LINKED HYALURONIC ACID HYDROGEL VS STERILE SALINE AND AMNIOTIC EYE DROPS

PREPUBLICATION DATA ACVO 2022

Cette étude pilote a démontré que l'AH réticulé BioHAnce TM permet une réduction significative du temps de cicatrisation (30-50%) comparé à des gouttes salines stériles et des collyres amniotiques utilisés dans un modèle murin présentant une lésion épithéliale cornéenne centrale standardisée. Ces résultats justifient la réalisation d'une étude plus approfondie pour évaluer de manière comparative l'impact des hydrogels sur le temps de cicatrisation de la cornée chez le chien.

Introduction

Hyaluronic acid and amniotic-based hydrogels have been shown to enhance corneal healing. Considering the importance of faster reepithelialization in corneal repair and patient comfort, the aim of this study was to compare the efficacy of BioHAnce™ cross-linked HA vs sterile saline and amniotic eye drops as well as to understand study group size to power future work.

Materials & Methods

Efforts were made to minimize the pain and discomfort of the rats according to the guidelines of the Association for Research in Vision and Ophthalmology (ARVO) Statement for Use of Animals in Ophthalmic and Vision Research. In addition, the investigation was approved by «Pequeno Príncipe Hospital Complex's Ethics in Animal Use Committee, Curitiba-PR, Brazil». In this model five rats were anesthetized via intramuscular administration of 10% ketamine hydrochloride at a dose of 50mg/kg and 2% xylazine hydrochloride at a dose of 10 mg/kg. They also received topical application of 0.4% oxybuprocaine hydrochloride eye drops. Following anesthesia, superficial keratectomy surgery was performed on both eyes.

The size of the corneal epithelial injury was pre-established and performed using a corneal trephine 3.0 mm in diameter. The area bounded by the trephine was then de-epithelialized with a corneal diamond burr (AlgerBrush II), thus generating a central corneal defect, as previously described by Portela 2021[6]. Corneal defects were then evaluated by fluorescein staining and imaged under a blue light immediately following the surgery (time point T=0), then at 12, 24, 36, 48, and 72 hours. Each animal had one eye that served as a control and received sterile saline drops at the same frequency as hydrogel drops. The other eye, the treated group, received 1 drop twice daily of BioHAnce™ cross-linked HA as prepared as previously described and provided in sterile eye drop bottles.

Data Analysis & Results

- The cornea was considered healed when there was no fluorescein staining on the corneal surface (Figure 1).

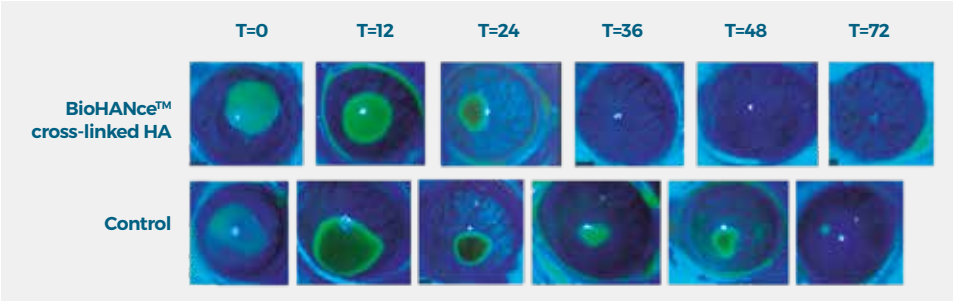


Figure 1. *Fluorescein imaging of corneal defects treated with cross-linked hyaluronic acid compared with control (no treatment) immediately following surgery in a rat, T=0 and at time points of 12, 24, 36, 48, and 72 hours.*

- A paired t-test statistical analysis was performed to compare the control group with the treated group. The treated group had a mean healing time of 48 ± 18 hours and the control group had a mean healing time of 67 ± 11 hours, although in several animals healing was not complete in the control group at the last time point. The healing time was significantly reduced (p=0.048) in the eyes treated with cross-linked hyaluronic acid (Figure 2).

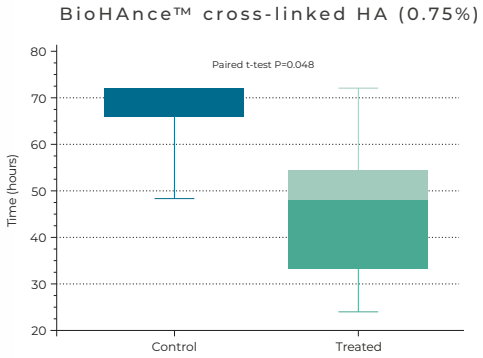


Figure 2. *Box plot of time to healing comparing control (no treatment) with cross-linked hydrogel (treated). Statistical significance from a paired t-test with a p value of 0.048, n=6. Study concluded at 72 hours, so no whisker variation is shown beyond that point.*

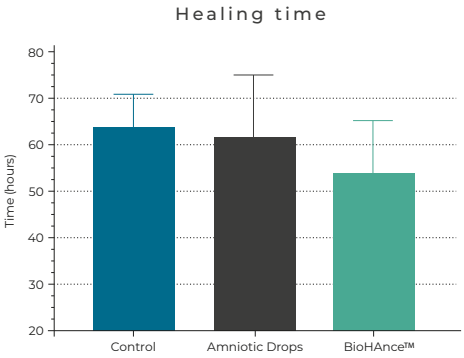


Figure 3. *Time to healing comparison of control to two different treatment groups (BioHAnce™ cross-linked HA and amniotic eye drops).*

Discussion

This proof-of-concept study supports that BioHAnce™ cross-linked HA contributes to increased healing rates (30-50%) versus control. Indeed, it is also worth noting that measurements for the study were formally stopped at 72 hours while it took over 100 hours to heal the cornea in the control group.

BioHAnce™ cross-linked HA showed a reduced healing time in comparison to amniotic eye drops. The difference was statistically significant. This result warrants further study into the comparative efficacy of hydrogels in corneal healing time in dogs.

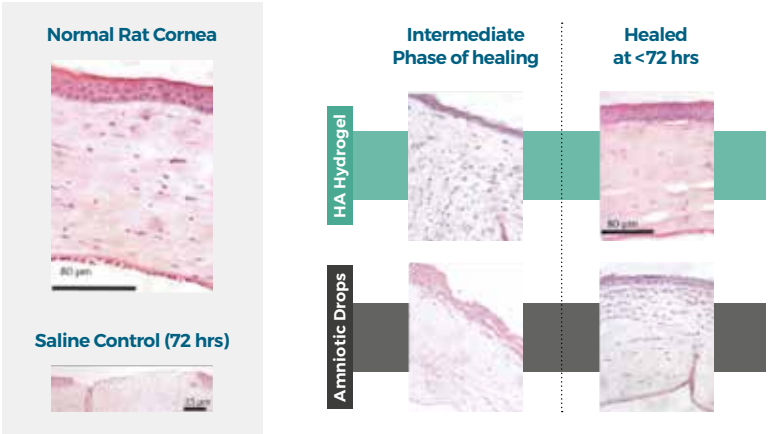


Figure 4. *H&E stained sections of normal rat cornea with no injury, saline treated corneal injury, intermediate phase of healing and fully epithelialized cornea injuries treated with either cross-linked HA hydrogels, BioHAnce, or amniotic eye drops.*

4

TOPICAL CROSS-LINKED HA-BASED HYDROGEL ACCELERATES CLOSURE OF CORNEAL EPITHELIAL DEFECTS AND REPAIR OF STROMAL ULCERATION IN COMPANION ANIMALS

WILLIAMS DL, WIROSTKO BM,GUM G, MANN BK (2017).
INVEST OPHTHALMOL VIS SCI. ; 58:4616-4622.

L'administration conjointe TID d'AH réticulé BioHAnce™ à 0,75 % et de chloramphénicol à 0,5 % a accéléré de manière significative le comblement (jusqu'à 34 %) des ulcères stromaux cornéens aigus chez les chiens et les chats par rapport à l'administration conjointe d'une solution d'AH linéaire à 0,3 % et de chloramphénicol à 0,5 %. En outre, l'application topique de l'AH réticulé a favorisé la cicatrisation d'ulcères cornéens chroniques (> 2 semaines) chez les chiens.

Purpose

The purpose of this study was to determine the safety of topical ocular administration of a cross-linked, modified hyaluronic acid (xCMHA-S) hydrogel, and its effectiveness in accelerating repair and closure of acute and nonhealing corneal ulcers in companion animals as a veterinary treatment and its utility as a model for therapy in human corneal ulceration.

Methods

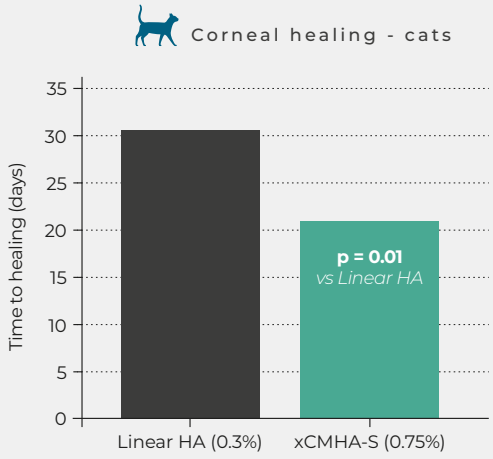
Two concentrations of xCMHA-S (0.4% and 0.75%) were topically administered to the eyes of rabbits six times daily for 28 days to assess safety. Then, 30 dogs and 30 cats with spontaneous acute corneal ulcers were treated with either xCMHA-S (0.75%) or a non-cross-linked HA solution (n = 15 per group for each species), three times daily until the ulcer had healed. Finally, 25 dogs with persistent nonhealing corneal ulcers were treated with xCMHA-S (0.75%) twice daily until the ulcer had healed.

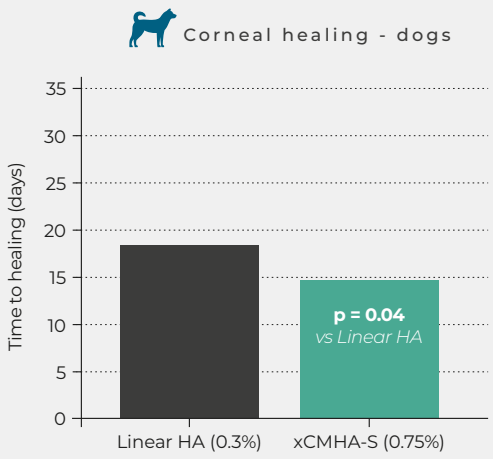
Results

Both concentrations of the xCMHA-S hydrogel were well tolerated, safe, and nontoxic in the 28-day exaggerated dosing study in healthy rabbits. Topically applied xCMHA-S significantly accelerated closure of acute corneal stromal ulcers in dogs and cats compared with a non-cross-linked HA solution. Furthermore, topical administration of the xCMHA-S aided in closure of nonhealing corneal stromal ulcers in dogs.

CONCLUSIONS

Hyaluronic acid has previously been shown to aid in corneal wound repair. This study demonstrates that a cross-linked, modified HA hydrogel provides additional benefit by accelerating time to corneal wound closure compared to a non-cross-linked HA solution in companion animals.





	xCMHA-S (0.75%)	iDrop linear HA (0.3%)	p
CATS	n=15 21.0 +/- 11.0 days	n=14 31.8 +/- 10.3 days	0.01
DOGS	n=15 14.8 +/- 4.1 days	n=15 18.3 +/- 4.9 days	0.04

Mean time to healing of acute corneal stromal ulcers in 30 dogs and 30 cats with topical chloramphenicol and three-times daily BioHAnce™ cross-linked HA (0.75%) or linear HA (0.3%)[4]

5

EVALUATION OF CROSS-LINKED HYALURONIC ACID GEL DROPS AND THERAPEUTIC COMBINATIONS FOR OPHTHALMIC INFECTIONS[7]

ACVO 2022 POSTER SESSION

Les propriétés physiques (viscosité, amincissement par cisaillement et concentration) de l'AH réticulé BioHAnce™ sont conservées lorsqu'il est associé à des antibiotiques ou antiviraux. Les résultats in vitro suggèrent que l'efficacité de la tobramycine est maintenue et que l'efficacité du ganciclovir est améliorée lorsqu'il est associé à l'AH réticulé BioHAnce™.

(SK Atzet[1], AD Fankhauser[1], EK Behan[1], BK Mann[1]) 1: SentrX Animal Care

Purpose

To evaluate the *in vitro* efficacy and physical properties of combining antibacterial and antiviral drugs with a patented cross-linked hyaluronic acid (XHA) based eye drops.

Methods

Several active pharmaceutical ingredients (Neomycin, Polymyxin B, Bacitracin, Gentamicin, Cefazolin, Ciprofloxacin, Gramicidin, Oxytetracycline, Tobramycin, Cidofovir, and Ganciclovir) were aseptically mixed with XHA, which, with its unique extracellular matrix, serves both as a delivery vehicle and eye lubricant. The resulting combined hydrogels were then evaluated for changes in physical properties (e.g., viscosity and shear thinning). Tobramycin hydrogels were evaluated for antimicrobial activity using a zone of inhibition assay. Ganciclovir hydrogels were tested for antiviral efficacy using a cytopathic effect assay (CPE) with Feline Herpesvirus 1 (FHV-1). Both were compared with the same drugs diluted in saline serving as controls.

Results

The addition of active ingredients resulted in no significant changes to the viscosity or shear thinning profile of XHA hydrogels. Tobramycin hydrogel and tobramycin control exhibited equivalent zone of inhibition against three strains of bacteria. XHA ganciclovir solution was found to have a 4.3 and 3.2 fold reduction of viral activity as compared with saline solutions of Ganciclovir.

CONCLUSIONS

In vitro results suggest that both the unique physical properties (viscosity, shear thinning, and concentration) of XHA and efficacy of tested active pharmaceutical ingredients are maintained or improved in the case of Ganciclovir. Future work will include target animal efficacy and disease state clinical studies along with application and dosing requirements based on potential synergistic effects from the XHA's increased residence time. Supported by SentrX Animal Care.

6

CROSS-LINKED HYALURONIC ACID ENHANCES TEAR FILM CONCENTRATIONS OF CEFAZOLIN SODIUM IN CANINE EYES[5]

ACVO 2023 CONFERENCE ABSTRACT - SUBMITTED FOR PUBLICATION

L'AH réticulé BioHAnce™ à une concentration de 0,75% a prolongé la persistance des concentrations élevées d'antibiotiques dans le film lacrymal de dix chiens sains. La concentration de céfazoline sodique dans le film lacrymal a été augmentée et des concentrations plus élevées d'antibiotiques dans le film lacrymal ont été maintenues plus longtemps (jusqu'à 8 heures) lorsque l'administration était associée à de l'AH réticulé BioHAnce™ à 0,75 %, comparativement à un lubrifiant oculaire moins visqueux.

(L Sebbag, E Ortaeskinaz, Y Goncharov, R Ofri, D Arad) Koret School of Veterinary Medicine, The Hebrew University of Jerusalem, Rehovot, Israel

Purpose

To compare tear film concentrations of cefazolin sodium when formulated with two different excipients/ lubricants.

Methods

Cefazolin sodium was compounded as a 5% solution using either 1.4% polyvinyl alcohol (PVA; Refresh®, Allergan) or 0.75% cross-linked hyaluronic acid (XHA; Oculenis®, Sentrx animal care). Ten ophthalmologically healthy dogs (5 brachycephalic, 5 non-brachycephalics; n = 20 eyes) received one drop of cefazolin-PVA in one randomly selected eye, and one drop of cefazolin-XHA in the other eye. Tear fluid was collected with 2-µl capillary tubes at times 0 min, 1 min, 5 min, 10 min, 15 min, 30 min, 60 min, 120 min, 240 min, 360 min and 480 min. Cefazolin tear concentrations were measured with UV-Vis spectrophotometry.

Results

No significant differences were noted in tear cefazolin concentrations between brachycephalic and non-brachycephalic dogs with either formulation at any time point ($P \geq 0.086$). In all eyes, mean tear film concentrations were significantly higher with XHA than PVA at all time points ($P \leq 0.049$) except for baseline and t = 60-120 min ($P \geq 0.105$). Tear film kinetics of cefazolin-XHA were somewhat 'biphasic', with drug levels decreasing from 0-120 min, then slightly increasing from 120-360 min prior to declining again until the end of the experiment (480 min). The area under the time-concentration curve ($AUC_{0\text{-}480}$) was 2.7 greater with XHA than PVA ($P=0.002$).

CONCLUSIONS

XHA greatly improved tear film concentrations of cefazolin sodium when compared with PVA, a less viscous excipient/lubricant. To dictate dosing regimens and determine clinical efficacy, future experiments should assess XHA-cefazolin in dogs with bacterial keratitis and determine clinical breakpoints for cefazolin against common bacterial pathogens of dog eyes. LS serves on the scientific advisory committee for the company that funded this study (Sentrx animal care).

EYE EXPERTS

En tant qu'expert international en ophtalmologie vétérinaire, Dômes Pharma s'engage à fournir aux vétérinaires, aux auxiliaires vétérinaires et aux propriétaires d'animaux de compagnie :

- Une large gamme de produits ophtalmologiques
- Notre expertise scientifique et technique
- Un support technique qualitatif constitué notamment de conduites à tenir et de formations

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