TANGY RE

SLIM

//zoneX: THE SCIENTIFIC STORY SO FAR...

ZONE

NICOTINE



COSMIC



→ INTRODUCTION

to save many lives if embraced.

While nicotine is an addictive substance that's not risk-free, science has demonstrated - and numerous public health bodies worldwide have recognised - it isn't the primary cause of smoking-related diseases. Rather, the combusting (burning) of tobacco creates smoke containing thousands of chemicals, many of which are harmful. These chemicals are then inhaled into the lungs of adult smokers.

Recent advances in technology have resulted in a range of innovative alternative non-combustible nicotine products, which we've termed Next

Our nicotine pouch product is called zoneX, and we believe it has a significant role to play in helping Imperial Brands make a meaningful contribution to THR.

TOBACCO HARM REDUCTION AND THE TOBACCO-FREE ORAL NICOTINE POUCH OPPORTUNITY

Tobacco Harm Reduction (THR) represents one of the most promising global public health policies with the potential

Generation Products (NGP). They all have the potential to be significantly less harmful than combustible cigarettes for those adult smokers who are either uninterested or unwilling to stop consuming nicotine. This concept underpins the foundation of THR.

Among these NGP are tobacco-free oral nicotine pouches. Free from tobacco leaf and harmful tobacco combustion, high quality oral nicotine pouches offer adult smokers an exciting and potentially harmreduced alternative to cigarettes.

LINE OF EVIDENCE #1

LINE OF EVIDENCE #2

LINE OF EVIDENCE #3

LINE OF EVIDENCE #4

LINE OF EVIDENCE #5

LINE OF EVIDENCE #9

\rightarrow INTRODUCING zoneX

Each zoneX pouch contains high purity pharmaceutical grade nicotine within a food-grade plant fibre-based substrate (e.g. wheat or bamboo), and other high-quality ingredients including food-grade flavourings, humectants to retain moisture, and additives to ensure product stability. By placing a pouch under the lip for up to 20 minutes, nicotine is released into the bloodstream via the gum lining (oral mucosa).

zoneX's appearance and oral method of use recalls conventional tobaccocontaining snus, itself a potentially harm-reduced product supported by favourable epidemiological data in Sweden (scan the QR code to learn more).

Critically, one vital difference makes zoneX distinct from snus: it's completely free of tobacco leaf.

As such, zoneX's THR potential relative to combustible cigarettes and snus may be even greater.

As part of our rigorous NGP Scientific Assessment Framework, we've produced a summary of the key research findings to-date. They substantiate zoneX's THR potential through nine key lines of scientific evidence (beginning on page 6.)

FIND OUT MORE..





NO TOBACCO

Users absorb nicotine via their gums, meaning any lungrelated toxicity and disease risks associated with smoking are not to be expected.



Manufactured using high purity pharmaceutical grade nicotine - free from tobacco leaf (and harmful tobacco combustion).

Contains high quality ingredients, including food grade quality



୍ୟା କ୍ର ଜ୍ୟା

OCOMBUSTIO,

flavourings.



Undergoes rigorous risk assessments by our in-house professional consumer safety toxicologists and other scientific experts to determine the suitability of ingredients and materials.



Doesn't produce harmful smoke (a by-product of tobacco combustion) or smell, so no impact on air quality or risk to bystanders.

LINE OF EVIDENCE #1

LINE OF EVIDENCE #2

LINE OF EVIDENCE #3

LINE OF

→ LINE OF EVIDENCE

Research shows zoneX contains substantially lower levels of harmful chemicals compared to combustible cigarette smoke, and even conventional tobacco-containing snus.

Tobacco smoke contains over 7,000 chemicals, around 100 of which are classified by public health experts as causes or potential causes of smoking-related disease.

All NGP provide a potentially less harmful alternative to combustible cigarettes because research shows they contain far fewer and substantially lower levels of harmful chemicals.

Our initial laboratory testing involved comparing the levels of 16 notable chemicals of public health interest (including NNN, NNK, formaldehyde, acetaldehyde, and benzo[a]pyrene) in zoneX compared to tobacco smoke and conventional snus.

As the chart overleaf illustrates, of these 16 chemicals 14 were not quantifiable at all, while 2 (acetaldehyde and formaldehyde) were detected at extremely low levels: .

- Compared to cigarette smoke, levels of acetaldehyde and formaldehyde were reduced by up to 99%.
- Compared to conventional snus, they were reduced by 74%.

Additionally, no microbial activity was detected in zoneX - while levels of mycotoxins (naturally occurring toxins produced by certain moulds/fungi) were not quantifiable.





Research shows substantially reduced in-vitro biological responses (mutagenicity, genotoxicity, and cytotoxicity) to zoneX compared to combustible cigarette smoke.

The next stage of zoneX's scientific substantiation involved using recognised regulatory methods to assess the product's impact on relevant cells compared to combustible cigarette smoke across three established regulatory assays.





Neutral red uptake (NRU) assay. Measures cytotoxicity, considered a potential step in several chronic disease processes associated with smoking - including cancer and emphysema.

In-vitro micronucleus (IVM) test. Measures genotoxicity, the damage to the structure or function of genetic material often mechanistically linked with the development of cancers.



Ames test. Assesses mutagenicity, which is the ability of substances to affect genetic material in cells.

CYTOTOXICITY

MUTAGENICITY

GENOTOXICITY

25%

zoneX #2 (5.8mg per pouch)

As the chart overleaf illustrates, zoneX demonstrated significantly reduced in-vitro responses compared to cigarette smoke in our studies. Under the conditions of test, it produced negative responses in both the IVM and Ames assays, while demonstrating only weak cytotoxicity relative to cigarette smoke in the NRU assay (>99% reduction).

Conversely, cigarette smoke induced a statistically significant positive response across all three assays.



We don't test our products on animals. Instead, we use cutting-edge, PETA Science-endorsed laboratory technologies in our NGP assessment. Scan the QR code to learn more about our alternatives to animal testing.

FIND OUT MORE





//09



In laboratory models, zoneX doesn't elicit skin sensitisation properties.

When our scientists used laboratory models to assess the gene expression profile of 200 markers in human cell lines, zoneX wasn't predicted to cause allergic reactions or skin rashes. This may be expected as our products contain only high quality, high purity ingredients.

\rightarrow LINE OF EVIDENCE 4

zoneX delivers nicotine to the blood of adult smokers via the oral mucosa, which on average has a lower and slower nicotine delivery compared to combustible cigarettes. This suggests it has a lower abuse liability compared to combustible cigarettes - although this shouldn't be interpreted as evidence that zoneX isn't addictive.

To achieve its THR potential, it's critical zoneX offers adult smokers a satisfying alternative to combustible cigarettes or conventional tobaccocontaining snus/modern oral chewing tobacco.

Effective nicotine delivery is therefore key to NGP adult smoker acceptance, and so assessing zoneX's performance in a controlled clinical setting forms the next stage of its scientific substantiation.

To understand how adult smokers' bodies absorb nicotine from zoneX pouches, how long it stays in their body, and how this compares to the blood nicotine delivery of smoking, we conducted two pharmacokinetic (PK) studies. The research involved 24 and 27 adult existing users of both oral nicotine products and combustible cigarettes trying a range of zoneX nicotine strength variants up to 20mg per pouch. The first study used a combustible cigarette comparator; the second a conventional (i.e. tobacco) snus comparator.

Both sets of clinical data demonstrated zoneX efficiently delivers nicotine to the blood of adult smokers; the first study also confirmed it didn't exceed the delivery profile of cigarettes.

We already know that - unlike smoking a combustible cigarette - zoneX doesn't deliver nicotine via inhalation. However, we also wanted to confirm that nicotine delivery took place via the gums (oral mucosa) rather than via the swallowing of saliva.

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LINE OF EVIDENCE #1 LINE OF EVIDENCE #2 LINE OF EVIDENCE #3 LINE OF EVIDENCE #4



This fact is evidenced in the blood nicotine delivery curves below that unequivocally show nicotine being absorbed via buccal absorption, with limited amounts - if any - being swallowed. Other findings included:



→ LINE OF EVIDENCE 5

zoneX offers a satisfying alternative to both combustible cigarettes and conventional snus, and reduces adult smokers' desire to smoke/use nicotine.

Analysing zoneX's blood nicotine delivery is just one branch of pharmacology. It's also essential to understand how adult smokers react after using zoneX (known as pharmacodynamics, or PD); in particular, their desire to smoke combustible cigarettes again and – central to realising THR – whether zoneX constitutes an acceptable smoking alternative. Following initial use of zoneX, both sets of our clinical research show significant reductions in desire to smoke combustible cigarettes or use nicotine compared to the baseline starting points (i.e. preceding any nicotine product use). zoneX clearly offers sustained reductions in desire to smoke, with maximum reductions in urges (TE-max) occurring at around 20-25 minutes and for up

When compared on a per pouch/per cigarette stick basis, zoneX has a maximum nicotine concentration (Cmax) lower than that of combustible cigarettes. zoneX pouches take longer to reach their maximum nicotine concentration (Tmax) compared to combustible cigarettes. This was, on average, achieved at 25 min - which was closely aligned with most consumers' usage time per pouch. If nicotine was absorbed via swallowing, this would generate a flatter and lower shaped curve - with limited nicotine delivery to the blood. Moreover, there was no secondary nicotine peak, which would have indicated some gastro-intestinal nicotine absorption had taken place through subjects swallowing.

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The Cmax and Area Under Curve (AUC, which denotes a subject's total exposure to nicotine per pouch) was - as expected - found to be broadly proportional to the nicotine content of the pouch (i.e. as nicotine strength increases, so do blood nicotine concentration levels) but less than combustible cigarettes. As the blood nicotine delivery from zoneX is on average lower and slower compared to combustible cigarettes, zoneX is likely to have a reduced abuse liability relative to combustible cigarettes. While this shouldn't be interpreted as evidence it's not addictive, the data indicate the relative addictive potential of zoneX is unlikely to be greater than combustible cigarettes among current adult smokers.



to four hours before returning to the starting levels. In contrast, for combustible cigarettes, subjects' desire to smoke again returned to baseline levels much sooner - within less than an hour. LINE OF EVIDENCE #1

LINE OF EVIDENCE #2

LINE OF EVIDENCE #3

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LINE OF

\rightarrow LINE OF EVIDENCE **5** (CONTINUED)





zoneX has an encouraging short-term safety and tolerability profile, with no serious product-related adverse events observed under the conditions of controlled clinical trials.

Our clinical data also demonstrate zoneX's favourable short-term safety and tolerability profile for nicotine strengths up to 20mg nicotine per pouch under the conditions of controlled clinical trials, with no serious adverse events or significant changes on subjects' blood pressure, pulse, heart measurements or general wellbeing observed or

reported throughout observation periods.

events were recorded (e.g. a case of the hiccups), though these were all mild, self-limiting and are commonly reported for nicotine-containing products.



Only a small number of mild adverse

No clinically significant changes in either laboratory safety samples, physical examinations, and cardiovascular measures were observed following zoneX usage.

LINE OF EVIDENCE #1 LINE OF EVIDENCE #2 LINE OF EVIDENCE #3 LINE OF EVIDENCE #4

LINE OF EVIDENCE #5



Adult smokers and non-smokers properly understand zoneX contains nicotine and is not risk-free, but is potentially less harmful than combustible cigarettes.

While our research to-date compelling potentially harm reduced alternative to continued tobacco smoking, we recognise it's also crucial adult smokers understand the nicotine pouch category offer a potentially harm reduced alternative

We therefore wanted to gather perceptions and behavioural data to

understand zoneX's perceived usage intended use by adult smokers and potential unintended use by nonsmokers. We therefore asked over 1,500 adult tobacco and nicotine UK about their perceptions toward

cancer and cardiovascular disease.

Adult tobacco and nicotine users and non users alike understand that – while not risk-free – zoneX likely presents a lower risk than continued smoking.*



90% of adult tobacco and nicotine users accurately perceive the potential health risks and hazards from zoneX based on labels and packaging.**

* Study of 1532 UK adults ** Study of 250 UK adults



non-smokers. There's little evidence it would serve as a gateway to regular nicotine use amongst nicotine naïve populations.

While it's encouraging to learn many adult smokers view zoneX as a facilitator of THR, it's also important the product isn't used by non-smoking populations - and particularly by youth - as this would reduce zoneX's THR potential at the population level.

Encouragingly, as the chart below illustrates, UK survey data reveals adult smokers are significantly more likely to try or purchase zoneX than both younger and older non-users, as well as long-term quitters.

Curiosity and possible intent to purchase zoneX appears very low



zoneX appeals overwhelmingly to adult smokers, with very low interest amongst

among non-smokers. As such, there's little evidence the product might serve as a 'gateway' to regular nicotine use or combustible cigarette smoking in nicotine naïve populations.

LINE OF EVIDENCE #1

LINE OF EVIDENCE #2

LINE OF EVIDENCE #3

LINE OF EVIDENCE #4

LINE OF VIDENCE #5



The main reason for adult smokers' interest and intent to purchase zoneX is for potential harm reduction, and to reduce health risks associated with combustible cigarette smoking.

Importantly, THR reasons appeared to be driving adult smoker survey respondents' motivation to try or purchase zoneX. "It might be less harmful to me than combustible

cigarettes" was by far the most popular answer.

Of the current adult smokers who

reported they would be likely to

purchase zoneX, almost two-thirds said they would use them to replace some - or all - of their cigarettes.

NICOTINE POUCHES...



\rightarrow CONCLUSION

Research shows zoneX contains substantially lower levels of harmful chemicals compared to combustible cigarette smoke, and even conventional tobaccocontaining snus.

Research shows substantially reduced in-vitro biological responses (mutagenicity, genotoxicity, and cytotoxicity) to zoneX compared to combustible cigarette smoke.

In laboratory models, zoneX doesn't elicit skin sensitisation properties.

zoneX delivers nicotine to the blood of adult smokers via the oral mucosa, which on average has a lower and slower nicotine delivery compared to combustible cigarettes. This suggests it has a lower abuse liability compared to combustible cigarettes - although this shouldn't be interpreted as evidence that zoneX isn't addictive.

* Please note we don't market zoneX as a smoking cessation product

We believe our nine lines of scientific evidence convincingly demonstrate zoneX's THR potential. To recap:

5 zoneX offers a satisfying alternative to both combustible cigarettes and conventional snus, and reduces adult smokers' desire to smoke/use nicotine.

zoneX has an encouraging short-term safety and tolerability profile, with no serious productrelated adverse events observed under the conditions of controlled clinical trials.

Adult smokers and non-smokers properly understand zoneX contains nicotine and is not risk-free, but is potentially less harmful than combustible cigarettes.

zoneX appeals overwhelmingly to adult smokers, with very low interest amongst non-smokers. There's little evidence it would serve as a gateway to regular nicotine use amongst nicotine naïve populations.

The main reason for adult smokers' interest and intent to purchase zoneX is for potential harm reduction, and to reduce health risks associated with combustible cigarette smoking. LINE OF EVIDENCE #2 LINE OF EVIDENCE #3

LINE OF EVIDENCE #1

LINE OF EVIDENCE #4

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LINE OF VIDENCE #9

\rightarrow CONCLUSIONS

The totality of our scientific research to-date, coupled with our continued commitment to robust product quality, stewardship and manufacturing standards - as well as the implementation of youth access prevention programmes - demonstrates zoneX's potential as a THR tool beneficial to population-level health. Further research is ongoing.

In the interim, we encourage governments and regulators to consider the promising body of scientific evidence from both zoneX and the wider oral nicotine pouch category.

Not only should nicotine pouches be regulated according to their risk relative to combustible cigarettes; they should also be publicly and actively endorsed with one clear message as satisfying and potentially less harmful alternatives for those adult smokers who would otherwise continue to smoke.

We believe that doing so will expediate and cement their potentially crucial contribution to THR and public health.

FIND OUT MORE





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