Protocol Full Title Prospective Trial:

Effect of interceptive strategies on the clinical outcome of impacted maxillary permanent canines.

Protocol Acronym/short title:

RCT Impacted canines.
Version and date of final protocol:
Version 4.0 d.d. 01 July, 2016.
UZ Leuven Clinical Trial Center number S59030

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Signatures

_____ _____

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Date

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In accordance with local laws of Participating Site:

- ☐ Participating Site/Investigator shall foresee in adequate insurance coverage for possible damages linked directly or indirectly to the patients' participation to the Study at Participating Site and shall provide proof of such certificate to Principal Investigator
- ☐ no insurance coverage for possible damages linked directly or indirectly to the patients' participation to the Study at Participating Site is needed

Participating Investigator hereby represents and warrants that it shall comply with the local laws of Participating Site applicable to clinical studies and will present this protocol to the local ethical committee if required by local laws.

_____ _____

Participating Investigator

Prof. Dr. Ali Alqerban Date

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1. Study Synopsis

Title of clinical trial	Effect of interceptive strategies on the clinical outcome of impacted maxillary permanent canines.
Protocol Short Title/Acronym	Impacted Canines
Sponsor name	UZ Leuven
Principal Investigator	Prof. Dr. Guy Willems
Medical condition or disease under investigation	Maxillary permanent canine impaction
Purpose of the clinical trial	Prospective interventional study of maxillary permanent canines using classic interceptive measures for preventing impaction
Primary objective	To define the most optimal interceptive action for prevention of maxillary permanent canine impaction
Secondary objective (s)	To predict the risk of maxillary permanent canine impaction in young children
Trial Design	International Prospective Interventional Study
Endpoints	Eruption of maxillary permanent canines into the occlusal plane of the dentition.
Sample Size Estimation	For 80% power, 78 subjects needed in each group (for a 50% (nCLA) and 75% success rate (nCLB)). To increase the amount of information for the development of a prediction model for success at 18 months (2nd aim of the study) we need to increase the sample to 100/group (300 patients in total).
Summary of eligibility criteria	Untreated impacted maxillary canines with incomplete root formation, no resorption, no syndromes, no radiotherapy
Maximum duration of interceptive treatment of a subject	6 months
Minimum duration of interceptive treatment follow-up of a subject	6-18 months
Version and date of final protocol	Version 4.0 April 18, 2016
Version and date of protocol amendments	

2. Background and rationale

Maxillary canines contribute significantly to the function and esthetics of the permanent dentition. Completion of their development occurs relatively late. The germs are situated high in the maxilla of three year old children and canine crowns are mesially and palatally inclined. During eruption, the canine migrates down and forward towards the occlusal plane, while the tooth becomes gradually more upright until it reaches the distal aspect of the lateral incisor root and the mesial aspect of the deciduous canine's root apex. Deviation from the standard path of eruption leads to maxillary canine impaction possibly affecting neighboring tooth structures, i.e. causing mild to severe root resorption. Unfortunately, the incidence of maxillary permanent canine impaction is 1 to 3% and its treatment often requires surgical intervention. The purpose of surgically exposing the canine is to enable correction of the pathological path of eruption by applying orthodontic traction guiding the canine to its natural position in the dental arch. Simple interceptive measures taken at early age such as maxillary arch expansion or deciduous canine extraction have been advocated as successfully interfering with the pathological eruption of maxillary canines, avoiding the need for surgery and reducing the orthodontic treatment time and complexity.

3. Trial objectives and Design

3.1. Trial objectives and definitions

The purpose of this study is to detect the differences, if any, between three well known, validated interceptive measures in case of maxillary permanent canine impaction, and to prospectively follow up on these treated patients until further permanent canine alignment in the dental arch is achieved. This long term follow up is necessary in order to evaluate the effects of the interceptive treatment on permanent maxillary canine eruption.

In the present study, a **maxillary permanent canine impaction** would be defined as the inability of this tooth to erupt, failure of eruption, deviation of the canine from its normal eruption pathway or retention of the canine in the maxilla.

Success of a particular interceptive measure would be defined as eruption of the canine without the need for surgical intervention and integrity of the adjacent teeth.

3.2. Primary endpoints

The primary objective is to search for the most optimal interceptive action to prevent maxillary permanent canine impaction.

3.3. Secondary endpoints

The secondary objective is to evaluate whether based on the observations of the present study prediction of maxillary permanent canine impaction in young children is feasible.

3.4. Trial Design

The present trial is a non-commercial prospective randomized controlled trial of patients presenting with permanent maxillary canine impaction. These patients are selected at the intake consultation of the department of Orthodontics, UZ Leuven. A panoramic radiograph is the standard radiographic examination procedure at this particular moment in time for visualization of dental development and associated pathology. Maxillary permanent canine impaction may be diagnosed based on this radiograph by analysing predefined parameters correlated with maxillary permanent canine impaction. In case of signs of mild to severe canine impaction, an additional standard long cone apical radiograph (LCAR) is taken radial to the dental arch at the estimated normal permanent canine position to detect possible root resorption of the adjacent lateral incisor and to document the vertical permanent canine position. A CBCT will only be taken in the following two cases: evidence of damage to the adjacent teeth and for the purposes of canine exposure surgery. Specific inclusion and exclusion criteria are described in paragraph 4.

Patients are stratified based on the presence of a cross bite (Group C) versus no cross bite (Group nC), either a frontal or a uni-/bilateral cross bite. Further categorization is performed for both groups C and nC into 3 subgroups, A, B and C, depending on the obtained parameters related to canine position and angulation. Subgroup CA contains the rather normally positioned canines, indicative for rather normal maxillary permanent canine eruption. This group will function as the control group within Group C. Badly positioned canines will be categorized into subgroup CB constituting the study group. Finally subgroup CC includes those canines that are extremely badly positioned (see paragraph 4) requiring specific additional action.

Cross bite group.

In line with normal standard treatment procedures, the **cross bite group** (Subgroups CA, CB and CC) will receive interceptive maxillary expansion (IME) using the standard techniques that are available and commonly applied in the university hospital. Patients in Subgroup CC, after receiving interceptive expansion treatment, will be further subjected to extraction of the deciduous canine (EX-III), whenever still present in the dental arch, and, depending on the severity of canine angulation and position, of the first deciduous molar (EX-IV). Decision for extraction of one or both of these deciduous teeth will be the responsibility of the treating dentist who will have to evaluate the clinical circumstances presenting in this patient with very badly positioned permanent maxillary canines (Subgroup CC).

After this IME intervention, including III-EX or not, all patients will be enrolled in a standard follow up protocol, requiring a maximum of 3 recall visits at 6, 12 and 18 months.

Non cross bite group.

The **non-cross bite group (Group nC)** will be further allocated in two groups based on the available space in the dental arch, commonly determined in the discipline of orthodontics with the Arch Length

Discrepancy (ALD) methodology: lack of space (subgroup L) versus normal adequate space (subgroup N) for tooth alignment in the dental arch. The lack of space subgroup L may show symptoms of inadequate space in the dental arch such as 'no spacing in the deciduous dentition', 'rotated maxillary permanent incisors', 'space lack for eruption of maxillary permanent lateral incisors', etc.
Both categories in this **non cross bite group (Group nC)**, -either lacking space or displaying normal adequate space for tooth alignment- will consist of four subgroups, including A, B and C, as detailed above, plus subgroup D, in the case of absence of deciduous maxillary canines (due to premature loss or extraction).

1. Non cross bite group with lack of space.
Patients without cross bite but lacking space in the dental arch are subcategorized into the following 4 subgroups:

Patients in ***Subgroup nCLA***, constituting patients with no cross bite present but lacking space for adequate tooth alignment in the dental arch, will be randomly attributed to one of our three usual treatment options, being interceptive maxillary expansion (IME), extraction of the deciduous canines (EXIII), or no treatment (CO). The latter will constitute the control group within Group nCLA, indicative for maxillary permanent canine eruption in case of lack of space in the dental arch. After this interceptive treatment, all the patients will be enrolled in a standard follow up protocol. In case of absence of deciduous maxillary canines, randomization will not be possible. These patients will still be treated with expansion because of the lack of space and will also be enrolled in subsequent follow-up.

Patients in ***Subgroup nCLB*** will also be randomly attributed to one of these three usual treatment protocols, being interceptive maxillary expansion (IME), extraction of the deciduous canines (EXIII), or no treatment (CO). The latter will constitute the control group within Subgroup nCLB. After this interceptive treatment, all the patients will be enrolled in a standard follow up protocol. In case of absence of deciduous maxillary canines, randomization will not be possible. These patients will still be treated with expansion because of the lack of space and will also be enrolled in subsequent follow-up.

Subgroup nCLC, constituting the patients with no cross bite present but lacking space for adequate tooth alignment in the dental arch and with very badly positioned and angulated permanent maxillary canine(s), will receive interceptive maxillary expansion (IME) using the standard expansion techniques described above and commonly applied in the university hospital. Patients in Subgroup nCLC, after receiving interceptive expansion treatment, will be further subjected to extraction of the deciduous canine at 6month follow-up, whenever still present in the dental arch, as well as, depending on the severity of canine angulation and position, of the first deciduous molar. Decision for extraction of one or both of these deciduous teeth will be the responsibility of the treating dentist who will have to evaluate the clinical circumstances presenting in this patient with

very badly positioned permanent maxillary canines. Sequence of eruption other than 3-4-5 will also constitute a criterion for extraction of these deciduous teeth.

After this interceptive treatment, which will last for a maximum of 6 months, all patients will be enrolled in a standard follow up protocol, requiring a minimum of 3 recall visits at 6, 12 and 18 months.

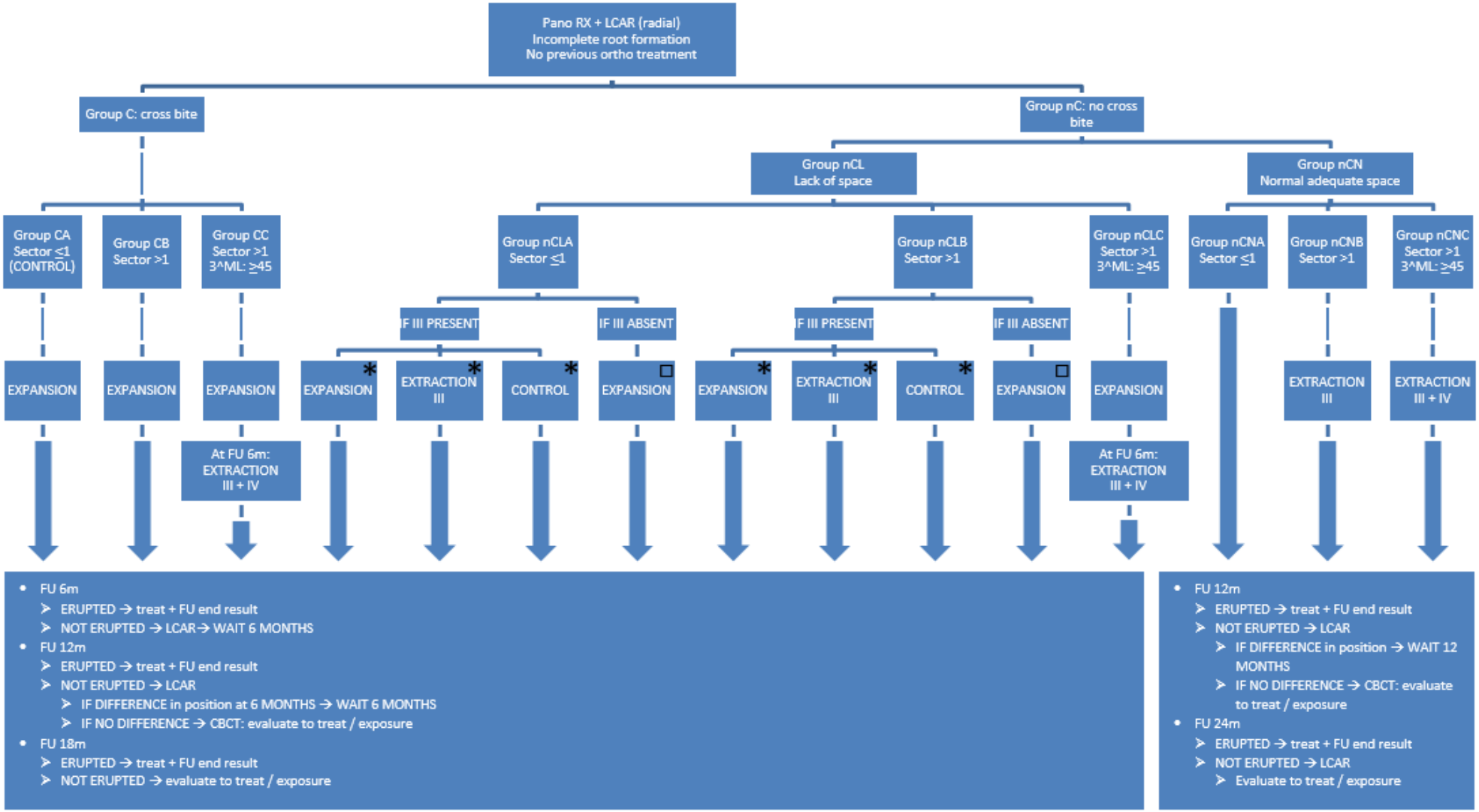
2. Non cross bite group with normal adequate space.

Accordingly, Group nCN will constitute all other eligible patients, consecutively seen at the first consultation of the Department of Orthodontics, with one/two impacted permanent maxillary canines without cross bite and showing normal adequate space in the dental arch for tooth alignment. Also these subjects will be categorized into the three subgroups A, B and C. They will receive no interceptive treatment (CO) at all except for subgroup nCNC, constituting of patients with normal alignment and adequate amount of space present but presenting with very badly positioned and angulated permanent maxillary canines. They will be further subjected to extraction of the deciduous canine (EX-III), whenever still present in the dental arch, as well as, depending on the severity of canine angulation and position, of the first deciduous molar (EX-IV). Decision for extraction of one or both of these deciduous teeth will be the responsibility of the treating dentist who will have to evaluate the clinical circumstances presenting in this patient with very badly positioned permanent maxillary canines. Sequence of eruption in the maxilla other than 3-4-5 (canine, first and second premolar) will also constitute a criterion for extraction of these deciduous teeth

After this intervention, all patients in this Subgroup nCN will be enrolled in a standard follow up protocol, requiring minimum one recall visit at 12 months for follow up of normal eruption, eventually a second one after 24 months, provided the maxillary permanent canine is not erupted yet, its root is still not completely formed and no other orthodontic treatment needs are present.

All subjects included in this trial will eventually be subjected to the described follow up procedures, which are described in more detail in Chapter 5. The follow up procedure is designed in order to detect positional changes of the permanent canine position, either spontaneous changes in the control group or changes associated with the interceptive measures taken. Follow up is a necessary and standard procedure for pointing out impacted canines and their true indication for surgical exposure of this tooth.

3.5. Study diagram



* = randomisation

□ = not randomised

3.6. Trial Flowchart

	Screen visit	Record collection	Third visit	Follow up 6 months	Follow up 12 months	Follow up 18 months	Follow up End result
Informed consent		X					
Physical/Oral examination	X			X	X	X	X
Clinical photograph (if needed)		X		X	X	X	X
Panoramic radiograph (if needed)	X						X
Long cone apical radiograph (if needed)	X			X	X	X	
CBCT scan (if needed)					X		
Identification as potential inclusion in the study	X						
Inclusion in one of the groups and randomized treatment assignment		X					
Start of the assigned treatment (expansion, extraction deciduous canine/molar or no treatment)			X	X	X	X	
Surgical exposure of the maxillary permanent canine					X	X	

4. Selection and withdrawal of subjects

4.1. Inclusion criteria

- General inclusion criteria:
  - Female or male patients coming to the department of Orthodontics of the UZ Leuven seeking for orthodontic advice.
  - Presenting with one or two non-fully erupted or impacted maxillary permanent canines (If bilateral impaction occurs, categorization into the different protocol groups will be based on the canine showing the worst position.)
  - Presenting with one or two maxillary permanent canines showing no more than ¾ root formation.
  - Any race
- In case of cyst around the area of the impacted canine, extraction of the persisting deciduous canine will be the treatment of choice. Also these cases will remain in follow up according to

our protocol but will not be randomized or attributed in one or other group.Specific canine related inclusion criteria for the allocation of patients in 3 different groups based on the presence of a cross bite (Group C), the absence of a cross bite with lack of space in the dental arch (Group nCL) and the absence of a cross bite with normal adequate space dimensions present in the dental arch (Group nCN):

- Group C (cross bite present)
  - Presence of a cross bite for all three subgroups: uni/bilateral/anterior cross bite. If end-to-end cross bite is present or tendency to cross bite, this will be considered as cross bite
  - Group CA: canine position sector ≤1.
  - Group CB: canine position sector >1.
  - Group CC: canine position sector >1, canine angulation towards the midline ≥45°.
- Group nCL (no cross bite present)
  - Absence of cross bite and lack of space in the dental arch.
  - Group nCLA: canine position sector ≤1.
  - Group nCLB: canine position sector >1.
  - Group nCLC: canine position sector >1, canine angulation towards the midline ≥45° .
- Group nCN (no cross bite present and normal space conditions in the dental arch)
  - Absence of cross bite and normal space conditions in the dental arch.
  - Group nCNA: canine position sector ≤1.
  - Group nCNB: canine position sector >1.
  - Group nCNC: canine position sector >1, canine angulation towards the midline ≥45° .

4.2. Exclusion criteria

- Fully erupted permanent canines
- Previous orthodontic treatment.
- Canines with completed root formation

- Evidence of root resorption of adjacent teeth or root malformation of the canines that would obligate to extract any adjacent teeth or the canine(s).
- Craniofacial syndromes
- Systemic disease that would impede orthodontic treatment/surgery
- Recent exposure to radiotherapy.

4.3. Expected duration of trial

The trial will start at the first screening visit, where physical/oral examination will take place. If needed, standard radiographic screening images will be taken as well. If the patient is identified as complying with the inclusion criteria, a second visit will be programmed for the collection of standard orthodontic records and randomization for inclusion in any of the groups. The assigned interceptive treatment will start on a third visit. After a maximum of 6 months of interceptive treatment, follow up visits will be scheduled after 6, 12 and 18 months. At any of those recalls, if the canine has erupted, the patients may opt to start regular orthodontic treatment with fixed appliances if needed or desired (average duration of 24 months) and a last follow up visit will be programmed after the end of this treatment for evaluation of the final canine position.

5. Trial Procedures

5.1. By visit

Screening visit

Patients come to our service seeking orthodontic advice. After physical/oral examination, a panoramic radiograph will be taken if considered necessary. Patients needing interceptive treatment and complying with the selection criteria will be identified.

Second Visit (Record taking)

Clinical photographs and orthodontic study casts, constituting normal orthodontic records for adequate diagnostics and treatment planning will be taken, as well as a standard long cone apical radiograph (LCAR) to determine the position of the canine. Depending on the obtained parameters related to canine position and angulation, the patient will be included in one of the groups detailed in chapters 3 and 4. The patient and parents will be informed about the need for treatment and they will be asked for consent when using the data for the purposes of the study. They will be given the informed consent, included in our regular contract for orthodontic treatment, with all the necessary details and information.

Third visit

If the patient decides to start treatment, the assigned treatment option will start (expansion, extraction of deciduous canine/molar or no treatment). Patients in the expansion group will be in treatment during a maximum of 6 months taking on average 4 and maximum 6 consultations. After

interceptive treatment with a removable expansion appliance, it might be necessary to wear the modified removable appliance at night for an extended period of 2 months.

Follow up 6 months

- If the canine has erupted, a revaluation of the specific presenting malocclusion will be performed and the need for further orthopedic or fixed appliance treatment will be discussed with the patient or his/her parents/guardians. Normal orthodontic treatment can be performed if desired. Only at the end of orthodontic treatment or, in case of no treatment need, at the end of late mixed dentition transition into permanent dentition, a last follow up visit will be planned in order to evaluate the end result.

- If the canine has not erupted yet, a long cone apical radiograph will be taken for evaluation of the canine position and reevaluation will take place after 6 months (= follow up visit 12 months).

Follow up 12 months

- If the canine has erupted, a revaluation of the specific presenting malocclusion will be performed and the need for further orthopedic or fixed appliance treatment will be discussed with the patient or his/her parents/guardians. Normal orthodontic treatment can be performed if desired. Only at the end of orthodontic treatment or, in case of no treatment need, at the end of late mixed dentition transition into permanent dentition, a last follow up visit will be planned in order to evaluate the end result.

- If the canine has not erupted yet, a long cone apical radiograph will be taken for evaluation of the canine position.

    - If a difference in vertical position is found when comparing with the LCAR taken during the last follow up visit, showing positive progression in canine eruption, revaluation will take place after 6 months (= follow up visit 18 months).

    - If canine position between 6 and 12 months follow up remains unchanged, a CBCT might be indicated to evaluate canine position and its relation to the neighboring teeth. Depending on the CBCT evaluation, it might be decided to surgically expose the canine, either via a closed or open technique depending on its position. When the canine is exposed, further active orthodontic treatment will be needed to guide the canine into its position in the dental arch. Only at the end of orthodontic treatment, a last follow up visit will be planned in order to evaluate the end result, being the final position of the maxillary permanent canine in the dental arch.

Follow up 18 months

- If the canine has erupted, a revaluation of the specific presenting malocclusion will be performed and, in case this should not have been made already, the need for further orthopedic or fixed appliance treatment will be discussed with the patient or his/her

parents/guardians. Normal orthodontic treatment can be performed if desired. Only at the end of orthodontic treatment or, in case of no treatment need, at the moment the canine reaches its final position in the dental arch, a last follow up visit will be planned in order to evaluate the end result.

- If the canine has not erupted yet, and positive progress was monitored at the 12 months follow up visit, a new LCAR will be taken to revaluate canine eruption process, unless clear clinical indicators are present witnessing successful path of eruption, i.e. clear bulging of the canine crown in the vestibulum or clear canine cusp morphology visible in the buccal mucosa. Patient will then be instructed to report for follow up appointment at the time of canine eruption into the dental arch or at the latest after 6 months, being an extra 24 months recall. Anyhow, at the 18 months follow up visit, a revaluation of the specific presenting malocclusion will be performed and the need for further orthopedic or fixed appliance treatment will be discussed with the patient or his/her parents/guardians. Normal orthodontic treatment can be performed if desired or needed at the time. In this case, further spontaneous canine eruption will be monitored during orthodontic treatment. Only at the end of this orthodontic treatment or, in case of no further treatment need, at the end of late mixed dentition transition into permanent dentition, a last follow up visit will be planned in order to evaluate the end result.

Follow up End result

As indicated above, two aspects of interceptive orthodontic treatment will be monitored. First of all the process of canine eruption being the maxillary permanent canine perforating the oral mucosa and erupting into the dental arch, and second the final position of the canine in the dental arch and its occlusion. Evaluation of the final result, eventually after orthodontic treatment, will include esthetics as well as functional occlusion and periodontal parameters giving an indication of gingival health. Assessment of the following parameters will be made: final position of the canine, final occlusion, root integrity of the canine and adjacent teeth, level of gingiva, general esthetic and functional result, gingival health. In order to do this, routine final records (clinical pictures, casts, LCAR or panoramic radiographs) will be taken as is performed for evaluation of standard orthodontic treatment.

5.2. Laboratory tests

Not applicable.

5.3. Other investigations

Not applicable.

6. Assessment of efficacy

- **Primary efficacy parameters**
  - Eruption of the canine
  - Integrity of the roots of adjacent teeth

- **Secondary efficacy parameters**
    - Improvement of canine angulation (root and crown tip)
    - In case of expansion or extraction of the deciduous canines:
        - Improvement of transversal and sagittal occlusion

7. Assessment of Safety

7.1. Specification, timing and recording of safety parameters

The following measures will be used to determine subject safety during the study:

- Physical/oral examination
- Radiographic examination
- Frequent follow up
- Adverse event reporting

7.2. Procedures for recording and reporting adverse events (AE)

Every visit is officially reported in the patient's file in order to identify possible problems and keep a track of them. In case of impacted canines, the major adverse event that could possibly occur is root resorption of the adjacent teeth, which is most of the time unpredictable and even inevitable. In case of such inevitable events, everything will be done to limit the possible damage, including prioritizing surgical exposure of the canine in an effort to reduce the damage, or even extraction of the lateral incisor/s in case of advanced root resorption. However, there is no evidence on existing predictors of this situation. In other words, resorption of the lateral incisors remains unpredictable.

7.3. Treatment stopping rules

Treatment or follow up will immediately stop when compliance of the patient becomes a problem or when for one or other reason, the patient or his/her parents/guardians want to discontinue follow up/treatment:

- The patient does not comply with treatment (does not follow the given instructions, misses the appointments).
- The patient's poor levels of oral hygiene compromise the health of the teeth and/or surrounding soft tissues.
- The patient wishes to stop treatment.

8. Statistics

Measures taken to minimize bias:

- Allocation concealment: randomization of the treatment options by a randomization list.
- Blinding measures: measurements of canine inclination on OPG will be taken by two operators, blinded to each other's measurements as well as to the name of the patient, treatment followed or occlusion details.
- Previous power calculation

8.1. Sample size

Randomisation into expansion, extraction and control will be applied for patients without cross-bite having lack of space and – based on canine position and angulation - belonging to strata nCLB and nCLA. Within each of both strata, a randomisation will be performed using permuted blocks of varying size, yielding an equal number of patients in each of the three groups.

Success of the approach is defined as eruption without necessity of surgical intervention and integrity of the roots of the adjacent teeth. The primary endpoint is defined as the percentage success after 18 months. The trial is powered to show a difference between any of the pairs of groups. To have at least 80% power to show a higher success rate in one group compared to the other group, there are 78 subjects needed in each group assuming a success rate of 50% in the first group and 75% in the second group. The calculation is based on a two-sided χ^2-test with alpha set at 0.05/3=0.0167 to control the family-wise error rate at 5% (3 pairwise comparisons). However, to increase the amount of information for the development of a prediction model for success at 18 months (cfr. second aim of the study) it has been decided to increase the number of patients to 100 per group (300 patients in total).

8.2. Analysis

The analysis of the primary endpoint will be based on a stratified χ^2-test using a Bonferroni-Holm correction to correct for multiple testing (the strata are nCLB and nCLA). The same approach will be used for the comparison at the earlier timepoints (6 and 12 months). No interim analyses are planned, neither for efficacy, nor for futility. The analysis will be performed on an intent-to-treat basis.

A multivariable logistic regression model will be used to predict maxillary permanent canine impaction (=lack of success) on all included subjects. A backward selection procedure will be applied with 0.157 as critical level for the p-value. This critical value corresponds to the use of the Aikake Information Criterion (AIC) for model selection. With AIC we require that the increase in model χ^2 has to be larger than two times the degrees of freedom. This strategy provides a trade-off between erroneous inclusion and exclusion of covariates in a prediction model (Sauerbrei W. The use of resampling methods to simplify regression models in medical statistics. Applied Statistics1999;48 (3):313–329.). The considered predictors are: strata formed by presence of cross-bite and parameters related to canine position and angulation, non-eruption, interceptive strategy, patient's age, stage of canine root formation, premature loss of deciduous teeth, familial history, space deficiency (arch length discrepancy).

As a sensitivity analysis, the prediction model will also be applied separately on the patients from the randomized and non-randomized part of the study.

9. Quality assurance

During this randomized clinical trial only standard operating procedures will be employed, such as i.e. removable expansion device, fixed expansion device, headgear, etc.. They are all validated, thoroughly described and widely used techniques. It will be up to the treating professional to decide for a given case which procedure to follow, in line with existing traditions in the specific collaborating centres. However, the main purpose should be attained which is expansion or in other words gaining extra space for tooth alignment. Depending on the interceptive treatment to be accomplished, decision will be taken to employ one specific treatment protocol to reach the goal set forward.

Randomisation will only be used when the different treatment options could be equally beneficial to the patient, with the objective of identifying possible differences in treatment outcomes. There is no new intervention to test, which minimizes the risk for negative impact.

10. Direct access to source data and documents

The investigators and the involved institutions will permit trial-related monitoring, audits, EC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents (i.e. patients' case sheets, X-ray reports, etc.).

11. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2013), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to the Ethics Committee of the UZ/KU Leuven for Clinical Trial Authorization.

The Study can and will be conducted only on the basis of prior informed consent by the Subjects, or their legal representatives, to participate in the Study. The Participating Site shall obtain a signed informed consent form (ICF) for all patients prior to their enrolment and participation in the Study in compliance with all applicable laws, regulations and the approval of the UZ/KU Leuven Ethics Committee. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the Study disclosed to Participating Site and/or Investigator in this Study as confidential and shall not disclose

such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data).

In this study, data will be coded.

*(Data are **anonymous** if no one, not even the researcher, can connect the data to the individual who provided it. No identifying information is collected from the individual.*
*When data are **coded**, there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers will be stored separately from their research data and replaced with a unique code to create a new identity for the subject, as coded data are not anonymous.)*

12. Data Handling

The patient's data (radiographs, follow up reports, …) will be stored in the patient's electronic folder, without linking it to the study. A randomization list will be electronically made in order to manage the allocation of the patients. Everything related to the University Hospitals Leuven patient treatment will be stored on the University Hospitals Leuven database. In case of further use of the data (for statistical purpose, etc.), the identity of the patients will remain anonymous.

13. Data Management

All data will be managed electronically, except for the informed consent (included in our regular contract for orthodontic treatment), a copy of which will be printed in paper for the patient and parents. A signed copy will be electronically saved with the rest of the data in the University Hospitals Leuven database.

14. Translational research

No biological material will be collected/shipped/stored/used for the study.

15. Publication Policy

As it is an international multicentre trial:

It is anticipated that the results of the overall Study will be published in a multi-centre publication, involving the data of all clinical sites participating in the Study.

The Participating Site is not allowed to publish any data or results from the Study prior to the multicentre publication, provided however that Participating Site is allowed to publish the results generated at the Participating Site if the multicentre publication has not occurred after 12 months from Study database lock.
Any publication by Participating Site will be submitted to the Sponsor for review at least thirty (30) days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.
Publications will be coordinated by the Investigator of Sponsor. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

16. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, University Hospitals Leuven shall assume, even without fault, the responsibility of any damages incurred by a Study Patient in the Leuven Centre and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

If an insurance coverage is required by local laws of Participating Site, the Participating Site shall have and maintain in full force and effect during the term of this Agreement (and following termination of the Study to cover any claims arising from the Study) adequate insurance coverage for possible damages linked directly or indirectly to the patients' participation to the Study at Participating Site.

17. Financial Aspects

There are no financial issues, meaning that this randomized clinical trial is not financially supported by any third party. Every Participating Site will manage its randomized clinical trial autonomously.