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Comments are especially welcome concerning preferred clinical endpoints / outcome measures and possible combinations hereto (6.3.4) and to the issue if placebo controlled trials (placebo on top of standard non pharmacologic treatment) are ethically justifiable in NDO (9.2.4).

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Keywords	***Urinary incontinence***

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Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Urinary Incontinence

Table of contents

Executive summary 5

1. Introduction 5

2. Scope 5

3. Legal basis 6

4. Main Guideline 6

4.1. Introduction 6

4.2. Background 6

5. Definitions and Diagnosis 7

5.1. Definitions 7

5.1.1. Stress Urinary Incontinence (SUI) 7

5.1.2. Urge Urinary Incontinence (UUI) 7

5.1.3. Mixed Urinary Incontinence (MUI) 7

5.1.4. Overactive bladder syndrome (OAB) 7

5.2. Diagnosis 7

5.2.4 Overactive Bladder Syndrome (OAB) 8

6. Study Design and Choice of Endpoints in Adults 9

6.1. Urodynamic and structural studies 9

6.2. Therapeutic exploratory studies and dose-finding studies (phaseII) 9

6.2.1. Design 9

6.2.2. Selection of patients 9

6.2.3. Choice of endpoints 9

6.3. Confirmatory studies (phase III) 10

6.3.1. Selection of patient populations 10

6.3.2. Blinding and randomisation 11

6.3.3. Choice of comparative therapy 11

6.3.4. Choice of endpoints 11

6.3.5. Timing of assessments and study duration 13

6.3.6. Evaluation of safety 13

7. Analysis 14

7.1. General approaches to analysis 14

7.2. Study type 14

8. Tissue engineering products (TEPs) for stress urinary incontinence 15
9. Urinary Incontinence in Children 16
10. Abbreviations 20

Executive summary

Following adoption of the *Note for Guidance on the clinical investigation of medicinal products for the treatment of urinary incontinence* (CPMP/EWP/18/01) it became apparent that some areas of the guideline would benefit from further explanation of the requirements for approval and for significant variations to the marketing authorisation.

Specific areas identified for revision were:

- A clarification of the terminology with regard to OAB (Overactive Bladder Syndrome) and respective registration requirements.
- A dedicated paediatric section.
- Outline of considerations for the development of a medicinal product for the use in stress incontinence.
- Inclusion of specific aspects on male incontinence.
- Specific considerations related to tissue engineered products used for this indication.

1. Introduction

The development of new agents and new formulations, routes of administration and/or regimens of existing agents for the treatment of urinary incontinence is recognised to be of importance to human health and wellbeing. These developments may provide new therapeutic approaches making use of novel technologies such as cell based medicinal products; improved diagnostic methods may lead to further elucidation of disease processes and better characterisation of target populations where treatments are likely to be beneficial.

Wherever possible, the revisions to CPMP/EWP/18/01 allow for some flexibility in order to facilitate drug development while ensuring that each indication sought is supported by sufficient data to enable a sound assessment of the benefit-risk relationship.

2. Scope

This guideline considers pharmacodynamic and clinical data required to support indications, dose regimens and durations of therapy for the treatment of urinary incontinence. It applies to the initial development programmes for new agents for the treatment of incontinence and to data generated to support additions and changes to the clinical elements of the marketing authorisation. A detailed description of the design of studies that might support individual types of indications is not provided.

The guidance is relevant to the development of medicinal products that are indicated for the treatment of the different forms of urinary incontinence in adult females, adult males and in the paediatric population. Such agents may be used in conjunction with other supportive measures and/or surgical procedures or as sole treatments. The guidance does also cover products derived from tissue engineering that are potentially indicated for the treatment of urinary incontinence. It does not cover incontinence related to local pathologies, such as infective, neoplastic, fistulous, metabolic or hormonal processes. An exception is incontinence associated with benign prostatic hyperplasia (BPH). Post voiding dribbling in males associated with BPH and nocturnal enuresis in adults is not covered by this guideline.

Although not specifically covered in this guideline, it is expected that much of the guidance (such as study design principles and outcome measures) will be used in the development of drugs for conditions

such as neurogenic incontinence, incontinence associated with radiotherapy, brachytherapy, cryosurgery, high intensity focused ultrasound (HIFU) for prostate cancer or radical cystectomy and neobladder. It is mandatory that separate studies are conducted for the investigation of medicinal products for the treatment of UI in patients with these conditions.

3. Legal basis

This guideline has to be read in conjunction with Annex I to Directive 2001/83/EC as amended, as well as all other pertinent EU and ICH guidelines and regulations.

4. Main Guideline

4.1. Introduction

Application dossiers should include a discussion of the overall content of the development programme that has been undertaken to support initial licensure or to support a variation to the marketing authorisation. It is not possible to provide specific and/or concise guidance in this document to cover every conceivable situation that may arise. Sponsors may find it particularly useful to discuss certain matters with EU Regulators before initiating various stages of the development programme. For example, the use of alternative study designs to those suggested, the choice of comparative regimens and the selection of non-inferiority margins.

It is recommended that the content of this Guideline is considered in conjunction with recent relevant documents issued by recognised societies in the fields of urology, gynaecology and paediatric urology. The influence of any such documents on the content of the clinical development programme may need to be discussed with EU Regulators and should be discussed in the application dossier.

4.2. Background

Urinary incontinence is a common and chronic condition affecting both males and females, although it is more commonly seen in women. While not life-threatening, urinary incontinence can have a significant negative impact on the psychological well-being, social functioning and overall quality of life of those affected. Prevalence varies greatly with age and the definition used, ranging from around 10 to 60%, not all of whom are in need of medical treatment. Women are considerably more commonly affected than men; for both genders, prevalence increases with age.

Women suffer most commonly from stress incontinence or a combination of stress and urge incontinence. Men suffer mainly from urgency and have a higher incidence of 'dry' symptoms (urgency, frequency without urinary incontinence), whereas stress incontinence accounts for less than 10% and is mainly attributable to prostate surgery.

Urinary incontinence also occurs in the paediatric population. Reported prevalence rates- depending on definition of the urinary problem and the population studied - range from around 1% to 8% decreasing with age. Urinary incontinence is usually reported to be slightly more common in girls than in boys.

While the overall prevalence of urinary incontinence and the prevalence of the different forms of urinary incontinence vary between genders, it is considered that the respective causes of the different forms of urinary incontinence in men and women are comparable in most cases and that the same methodological principles and outcome measures can generally be applied. However, exceptions are

made in cases where the aetiology is strictly gender specific (e.g. urge urinary incontinence associated with benign prostatic hyperplasia, BPH).

In young children the ongoing development of the urogenital system presents a special situation requiring specific methodological approaches. There are also considerable differences in aetiology, clinical presentation of signs and symptoms and appropriate outcome measures compared to the adult population. Urinary incontinence in children is therefore discussed in a separate part of the guidance.

5. Definitions and Diagnosis

5.1. Definitions

The two main types of incontinence are stress (effort) and urge incontinence. The term mixed incontinence denotes the concomitant appearance of stress and urge incontinence.

The International Continence Society, ICS, (2001) has published definitions at symptom level for the different forms of incontinence in adults, as summarised below:

5.1.1. Stress Urinary Incontinence (SUI)

Stress urinary incontinence is the complaint of involuntary leakage on effort or exertion, or on sneezing and coughing.

5.1.2. Urge Urinary Incontinence (UUI)

Urge urinary incontinence is the complaint of involuntary leakage accompanied by or immediately preceded by urgency.

5.1.3. Mixed Urinary Incontinence (MUI)

Mixed urinary incontinence is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing.

5.1.4. Overactive bladder syndrome (OAB)

Overactive bladder syndrome is defined as urgency with or without urge incontinence, usually combined with frequency and nocturia. In men, OAB is frequently associated with benign prostate hyperplasia (BPH).

It should be noted that the term "detrusor overactivity" is still used as a urodynamic-based definition that describes a particular type of detrusor dysfunction during filling cystometry. Detrusor overactivity may be further qualified as neurogenic detrusor overactivity, caused by a relevant neurological condition, or idiopathic detrusor overactivity when there is no defined cause.

5.2. Diagnosis

Urinary incontinence may be diagnosed at three different levels:

- as a symptom voiced by the patient (equals the ICS definition)
- as a sign observed by the physician using simple means to verify the symptom

- as a condition, defined by the presence of urodynamic observations associated with symptoms or signs.

The diagnostic criteria that can be considered sufficient for the purpose of clinical studies during drug development may have to be tighter than those applicable in normal clinical practice. A definitive diagnosis cannot usually be made based on symptoms only. This is particularly relevant for phase II studies where proof of concept for the investigational product must be demonstrated (see section 6.2).

5.2.1. Stress incontinence

Symptom: Involuntary leakage on effort or exertion, or on sneezing and coughing

Sign: Investigator-observed urinary leakage from the urethral meatus synchronous with effort, e.g. coughing or straining.

Condition: Urinary leakage during increased abdominal pressure without concomitant increase in detrusor pressure (this requires the simultaneous recording of abdominal and bladder pressures).

5.2.2. Urge incontinence

Symptom: Involuntary leakage accompanied by or immediately preceded by urgency. Urge incontinence is often associated with an increased frequency of micturition and episodes of urgency not leading to incontinence.

Sign: There is no directly and reliably observable sign of urge incontinence. Pad tests may verify leakage and diaries document episodes of urge incontinence, urgency and micturition frequency and volumes.

Condition: Involuntary detrusor contractions associated with urgency are observed during filling cystometry. This requires the concomitant registration of abdominal and bladder pressure. Urethral pressure should preferably also be monitored, as a drop in urethral pressure, representing a premature micturition reflex that may precede a detrusor contraction associated with urgency. The symptoms and signs of urge incontinence often appear in patients with a normal filling cystometrogram.

5.2.3. Mixed incontinence (MUI)

Symptom: Mixed urinary incontinence is the complaint of involuntary leakage associated with urgency and also with exertion, effort, sneezing or coughing (ICS definition)

Sign: Signs of both stress and urge incontinence (see above) are observed.

Condition: The conditions of stress and urge incontinence (see above) are both present.

5.2.4. Overactive Bladder Syndrome (OAB)

Symptom: Urgency with or without urge incontinence, usually combined with frequency and nocturia.

Sign: There is no directly and reliably observable sign. Pad tests may verify leakage and diaries document episodes of urge incontinence, urgency and micturition frequency and volumes.

Condition: Urodynamic testing characteristics do not reveal uniform test results among individuals with identical complaints. Therefore, OAB cannot be defined at condition level.

6. Study Design and Choice of Endpoints in Adults

6.1. Urodynamic and structural studies

Urodynamic studies may be useful at several stages of product development. Urodynamic phase (I-) II studies can elucidate the mechanism of action of an investigational product and may help identifying the target population most likely to benefit from treatment. The results of these studies could also be expected to be helpful in choosing the dose or dose range as well as endpoints for phase II and III studies.

Urodynamic studies aim to reproduce patient symptoms in a monitored setting. They are hence recommended in addition to history and clinical examination to confirm the diagnosis for the purpose of regulatory studies where possible.

At least in a subset of the study population, urodynamic studies are also considered useful as supportive parameters in the evaluation of the study outcome, e.g. where patients with clinical improvement can be demonstrated to have improved urodynamic parameters. In the case of clinical non-responders, urodynamic studies may contribute to failure analysis.

There are however significant limitations to this type of study: Interpretation is subjective and urodynamic data are poorly reproducible. Tests should be interpreted by at least 2, preferably 3, qualified, independent reviewers. It is highly important that the standardisation of test procedures as recommended by the ICS is employed when performing and interpreting urodynamic studies.

6.2. Therapeutic exploratory studies and dose-finding studies (phase II)

6.2.1. Design

Parallel group design including one placebo arm is recommended (see also 6.3.3 and 7.2). The duration of phase II studies should be long enough to include the time for reaching maximal effect, a study duration of six weeks is considered the minimum acceptable time and several doses should be studied to establish the effective dose.

6.2.2. Selection of patients

The highest level of diagnosis ("condition", see section 5.2.) is generally recommended in phase II studies. It is preferred that men and women are investigated in separate studies. Stress and urge incontinence should be studied separately.

If a drug is intended for use in patients with urinary urgency and increased urinary frequency but with no incontinence (the urgency-frequency syndrome without incontinence according to ICS), such patients should be studied separately.

Urinary incontinence in men associated with benign prostatic hypertrophy (BPH) is distinct from other forms of incontinence and must be studied separately.

6.2.3. Choice of endpoints

It is expected that the primary endpoint in therapeutic exploratory studies (phase II) is an appropriate urodynamic parameter as it is essential that proof of concept is demonstrated. An exception is OAB, which is not defined at condition level. Here, an appropriate clinical endpoint (see section 6.3.4) should be used. In men, pressure-flow studies may be necessary to exclude obstructive causes. In addition,

symptoms and signs (e.g. incontinence episodes, urinary frequency, urinary urgency, volumes voided etc) should be evaluated as secondary endpoints. The clinical endpoints should be chosen in analogy to the recommendations for phase III studies (see section 6.3.4.). It is not expected that all endpoints will be used in all studies. The selection to be used may vary with the aim of the study but should be scientifically justified in each case.

The types of urodynamic studies to be used differ between different forms of incontinence and depend on the goal of the study. Urodynamic procedures and the interpretation of findings should be strictly standardised in line with ICS requirements and applied by all participating centres. Secondary pharmacodynamics should be studied as appropriate for the drug substance.

The following section lists a number of acceptable urodynamic endpoints that may be used in phase II studies.

6.2.3.1. Stress incontinence

Urethral pressures at rest (maximum urethral [closure] pressure, urethral [closure] pressure profile, functional profile length) provide basic data on urethral closure function. Closure function is, however, the result of a complex interplay between the urethra and surrounding tissues during an increase in abdominal pressure (stress/effort). The effect of the medicinal product on urethral closure function during an increase in abdominal pressure can be studied by measuring abdominal leak point pressure (LPP). LPP denotes the abdominal pressure increase needed for incontinence to appear. The pressure increase may be brought about by a series of coughs of increasing intensity (cough induced LPP) or by Valsalva provocation (Valsalva LPP). Abdominal pressure measurement may be obtained vaginally, rectally or in the bladder. It is preferred that the appearance of leakage should be detected by a video-urodynamic method.

6.2.3.2. Urge incontinence

Cystometry may give information on effects of bladder sensation during filling, and aims to detect abnormal detrusor activity, bladder capacity and bladder compliance.

6.2.3.3. Mixed incontinence

For the indication mixed incontinence, urodynamic studies on both stress and urge incontinent patients should be made to demonstrate an effect of the drug on both components.

6.3. Confirmatory studies (phase III)

6.3.1. Selection of patient populations

The diagnostic level used as a study entry criterion should be defined and stated. Diagnosis at the sign level is acceptable in large phase III multicentre trials. In urge incontinence, this requires that symptomatic effect has previously been shown in patients both with and without detrusor contractions during filling cystometry as these patients may have different etiologies for their symptoms.

It is recommended to primarily include patients with ”pure” stress or urge incontinence to studies of stress or urge incontinence. For practical reasons it is, however, often necessary to include patients with mixed incontinence in both kind of studies. It is important that the kind of incontinence to be studied is the major complaint of the patient. Disease severity should be clearly defined using recognised grading systems and sponsors ensure that the target population is adequately reflected in the study population.

Patients with OAB likely to be associated with benign prostate hyperplasia must be investigated in a separate study. BPH must be treated optimally pharmacologically (with alpha-1 adrenoreceptor antagonists alone or in combination with an 5-alpha reductase inhibitor) or surgically, and results of the treatment for BPH should have been stable for 6 months before enrolment.

Elderly patients, specified as >65 years of age and >75 years of age, should be included in phase III studies in sufficient numbers to permit conclusions to be drawn on efficacy and safety in the elderly.

6.3.2. Blinding and randomisation

Randomisation and concealment of allocation is considered essential. All studies should be double-blind unless this design is considered to be impossible. Single-blind, evaluator-blind or open studies are considered to be less reliable than double-blind studies, especially when the judgement of outcomes is primarily based on investigator assessments of the clinical response. If a double-blind study is not feasible every effort must be made to ensure that the physicians who assess clinical outcomes remain unaware of treatment assignments.

6.3.3. Choice of comparative therapy

Studies of stress incontinence should be placebo controlled. Comparisons with non-drug and non-surgical therapies (e.g. pelvic floor exercise, vaginal devices) are encouraged but may pose problems with study design. Comparison with approved drug therapies for stress incontinence could provide additional information but is not considered mandatory. A possible approach is a 3 arm study comparing the investigational product to placebo and an active comparator (see section 7.2.1).

Drugs intended for the use in urge incontinence should equally be tested in placebo controlled trials as available drugs for urge incontinence do not consistently show superiority over placebo. A comparator arm including the best available treatment may be added to allow demonstrating superior efficacy or safety.

6.3.4. Choice of endpoints

The aim for developing new drugs for urinary incontinence should be to obtain improvement or cure of symptoms for the patient, hence patient scoring should constitute the primary endpoint in phase III trials. Changes in quantitative symptom measures allow a quantification of changes but cannot serve as surrogate endpoints for perception of effect. At least two quantitative symptom variables are expected to be used as co-primary endpoint.

The choice of (co)- primary endpoints may vary between studies and will depend on the aim of the study and the inclusion criteria. For stress incontinence the incidence of incontinence episodes and/or amount of urine leaked may be used. For urge incontinence the incidence of urgency, the frequency of incontinence episodes, and/or amount of urine leaked and/or the frequency of micturition are recommended as co-primary endpoints. The latter may be chosen in patients with urgency without incontinence. Other quantitative variables may provide supportive evidence and should be used as secondary end-points.

In stress incontinence, the proportion of patients requiring subsequent surgery may serve as an informative endpoint.

Wherever meaningful urodynamic measures are available, these can be used to support clinical findings.

It is important to note that it is generally not sufficient to demonstrate statistically significant improvement in the chosen outcome measures. It has to be demonstrated that the documented improvement in symptoms or symptom score is clinically relevant. A clinically relevant degree of improvement in the (co)- primary endpoint should be pre- specified and taken into consideration when determining the sample size.

The following section lists a number of possible endpoints that can be used in phase II and III studies. It is not expected that all endpoints will be used in all studies. The selection to be used may vary with the aim of the study, but should be thoroughly justified in each case.

Patient reported outcome measures

The overall outcome of treatment as perceived by the patient should be recorded by simple scales that are easy for the patient to use.

Symptom driven questionnaires may be used provided they have been validated. Clinical relevant changes should be determined, making a responder analysis possible.

Quantitative outcome measures

The following outcome measures can be used as quantitative efficacy endpoints in studies intended for registration of the product. The measurements may vary between different indications intended and should be kept in a diary for evaluating the effectiveness of treatment. The clinical relevance of the selected measures should be justified. Endpoints should be chosen from those listed below and justified as being the most appropriate to demonstrate a clinically relevant effect for the drug under investigation.

- the time (frequency) of micturitions
- the volume of each micturition
- the occurrence of incontinence
- number of nocturnal voids
- the occurrence of episodes of urgency without incontinence
- the number of protective pads used
- the amount of urine leaked in each protective pad (see below)
- Time to a clinically relevant relief of the incontinence symptoms

The information gathered using the above parameters allows calculating quantitative data and their change during treatment.

A diary including only recording of events (micturition, leakage, urgency and pad use) should and could usually be kept for a complete week. A diary including measuring of volumes and pad weight increase should be kept for as long a period as possible, usually for 48-72 hours but never less than 24 hours.

The symptom of urgency can be defined as "the sudden compelling desire to pass urine, which is difficult to defer". This is a rather vague definition that is open to different interpretations. Investigators are encouraged to use more descriptive terms for the degree of urgency felt by the patient at each micturition.

The circumstances under which the diary is kept should be approximate to those of everyday life, and should be similar before and after intervention to allow for meaningful comparison.

Pad weighing tests

By weighing protective pads before and after use, the amount of urine leaked into the pad can be measured. In this way urinary leakage can be quantified.

Pad weighing tests can be divided into short-term tests, generally performed under standardised conditions, and long-term tests, generally performed by the patient at home during 24-48 hours.

Reproducibility of the tests improves if the circumstances are standardised as much as possible (e.g. bladder filling in short term tests and activities in long term tests). For long term tests reproducibility increases with the length of the period measured.

Other objective endpoints

Other objective endpoints (such as Patient's Perception of Intensity of Urgency Scale, PPIUS) are also possible but then the dossier should include a scientific rational for the selected endpoint. Attention should be paid to the clinical significance of the effect.

Quality of life

Disease specific and generic instruments for measuring health-related quality of life (HRQL) can be used in trials of products for urinary incontinence. The instruments used should be properly validated in the target population. A clinically relevant change in prespecified domains (dimensions) of QoL should be defined and justified in the protocol of the study.

HRQL data should be considered an extension of an evaluation of efficacy, which can provide meaningful information to the prescriber and the patient. HRQL data can, however, never be the sole basis for efficacy claims.

Complication or worsening of the symptoms or de novo appearance of new urinary symptoms must also be recorded and investigated.

6.3.5. Timing of assessments and study duration

To allow appropriate evaluation of both safety and efficacy of an investigational drug, a study duration of at least 6 months is expected. The evaluation of the primary endpoint should occur at the end of the 6 month study period, when the full treatment effect can be expected to be evident. To provide an adequate safety database, a further follow up of at least 6 more months is necessary; this may be performed as an open label design if appropriate justification can be provided.

6.3.6. Evaluation of safety

Since urinary incontinence is a chronic disorder, safety data covering at least a 12 month period are required and long-term safety of new therapeutic interventions has to be established. The total clinical experience should generally include data on a large and representative group of patients in line with the guideline on population exposure (ICH E1A). Depending on specific pharmacokinetic characteristics, clinically important potential drug interactions should also be recorded.

As drugs for urinary incontinence will be used by the elderly, special efforts should be made to include a sufficient number of individuals over age 75 in clinical trials, particularly for safety reasons.

As drugs intended for use in urinary incontinence may affect bladder emptying, it is important to monitor patients for increased residual urine and urinary tract infections apart from general adverse event monitoring. Depending on the mode of action of the investigated treatment, special attention may have to be paid to long-term effects on different organ systems. Prostate cancer monitoring should be considered if hormonally active substances are investigated.

The number of patients to be studied will depend on the safety profile of each product and intended condition.

7. Analysis

7.1. General approaches to analysis

The primary analysis population should be the ITT population. Analyses of outcomes based on the (co-) primary efficacy variable should be performed in and compared between each of the pre-defined patient populations to assess consistency. In all studies there should at least be a comparison between the primary analysis and an analysis of all randomised patients in which indeterminate or missing outcomes are counted as failures as it is expected that a relevant number of patients will drop out of the studies due to lack of efficacy. Any incongruities detected between analyses should be explored and discussed. Other pre-planned analyses may include, among others, outcomes according to age, gender, difference in pathophysiology and other factors relating to patient management. Additional analyses should be planned and performed according to the designated secondary efficacy variables.

Efforts should be made to evaluate compliance with the study medication and reasons for non-compliance should be documented.

A clinically relevant cut-off for the proposed primary endpoint has to be defined. A responder analysis should be performed. The number or percentage of responders is a measure of the clinical relevance of the effect. Regulatory advice should be sought if there is uncertainty regarding the relevance of targeted clinical improvement.

7.2. Study type

Superiority versus placebo in well-conducted randomised studies is recommended. There is a strong behavioural component to urinary incontinence, and enrolment in a clinical study itself may make subjects more aware of their voiding habits and potential risk factors, making urinary incontinence studies susceptible to a significant placebo effect. The absence of a placebo control arm even in actively controlled trials in UI would require very sound justification and should be discussed with the regulatory authority in advance.

It is recommended that placebo-controlled studies should incorporate a third study arm that is randomised to an active comparator. The difference between the comparator and placebo can be used to help assess the clinical relevance of the difference between the test agent and placebo. For example, if the test agent has performed better than the comparator it is more straightforward to assume that the test agent provides a clinically relevant benefit. If the comparator has not demonstrated statistical significance over placebo or has not performed as expected from past experience the results observed with the test agent compared to placebo would have to stand alone. Inclusion of an active comparator can also help inference when the test agent fails to demonstrate superiority over placebo (i.e. a failed study) as it provides information on the assay sensitivity.

Noninferiority trial designs would only be appropriate if there was adequate evidence of a defined effect size and if there was sufficient assay sensitivity for the control treatment so that the proposed non inferiority margin can be supported. Until treatments are available for at least one of the forms of urinary incontinence where that is the case, noninferiority studies for regulatory purposes are discouraged. Even if there was an appropriately licensed treatment, the issue of assay sensitivity would still need to be fully addressed. An exception may apply where it is considered ethically impossible to

enrol patients into a placebo arm. In such cases, regulatory advice must be sought before commencing the study.

8. Tissue engineered products (TEPs) for stress urinary incontinence

8.1. Background

There is an ongoing interest to develop tissue engineering products (TEP) for the treatment of urinary incontinence. While sling surgery and retropubic colpo-suspension surgery is reported to have a success rate of continence in up to 80 % of patients after 1 year, it can be demanding for the patient and has both early and late complications. The success rate of injecting bulking agents to compress the urethra is considerably lower and there is a lack of GCP-compatible studies for this kind of treatment. Other available options are non-surgical and non-pharmacological treatment options (such as various devices and pelvic floor muscle training) but their effect size is rather limited and lacking the long term persistency.

Various products derived from autologous skeletal muscle cells have so far been investigated for the purpose of treating stress urinary incontinence but other types of tissue or cell products, autologous or homologous, may be developed for the treatment of urinary incontinence in the future.

Depending on their individual characteristics, cell based medicinal products (CBMPs) can have different clinical effects. Therefore all relevant clinical effects should be addressed in clinical development and existing authorized therapies and standard of care treatment should be considered. If bulking effect is one of the aims, it should be separated from the regeneration of the muscle tissue and both of these effects should be followed.

8.2. Exploratory and dose-finding studies (Phase II)

Appropriate dose finding study/(studies) needs to be undertaken. Size of individual dose as well as intervals of dose repetition in case of multiple dosages, and mode and site of administration are factors that need clarification.

The study product should be superior to the comparator. The comparator should be chosen based on the intended claim. An approved effective surgical or nonsurgical therapy should be the comparator or, if appropriate, placebo/sham. In case of no generally approved and accepted therapy for the condition studied, standard of care should be the comparator.

For exploratory studies alternative designs may be considered if appropriately justified.

8.2.1. Urodynamic and structural studies

For the development of a tissue engineered product, the urodynamic studies in phase II (see section 6) should be complemented with structural studies. Structural studies could confirm the main exploratory findings on structural changes on regeneration, such as:

- Rhabdosphincter´s volume
- Rhabdosphhincer´s thickening
- Rhabdosphincter´s contractility
- Integration of the newly formed tissue into surrounding muscle tissue

Study duration

For the purpose of TEP, a study duration of at least 6 months in phase II should be necessary. Depending on the type of products, the study duration may have to be extended to 12 months.

8.3. Confirmatory studies (phase III)

8.3.1. Selection of patients

Patients should be stratified by relevant baseline characteristics (e.g. underlying diagnosis and previous medical treatment, surgery or radiotherapy). Patients with clinically relevant urethral strictures should be excluded.

8.3.2. Study duration

In therapy development in SUI using TEPs, the minimal study duration of phase III studies should be 1 year premarketing with a mandatory follow-up for 2 years postmarketing, with focus on safety aspects. Other study duration for efficacy studies might be possible if appropriately justified.

8.3.3. Study type

For the TEPs in SUI, the superiority against standard of care should be shown.

8.3.4. Endpoints

For the confirmatory studies, the same efficacy endpoints should be applied for tissue engineered products as for other medicinal products developed for the treatment of urinary incontinence. Additionally to this, the structural endpoints should be considered as (co)- primary endpoints or as main secondary ones. For SUI indication, only the patients with pure stress incontinence should be included in such studies. Patient selection and study endpoints must be appropriate to show efficacy for the indication sought.

8.4. Scientific advice

It is recommended that European scientific advice is sought on a case by case basis, particularly concerning the choice of comparator, the type of analysis, and in coherence with the quality part of the cell based medicinal products (CBMP) and supportive non-clinical data.

9. Urinary Incontinence in Children

The most common forms of urinary incontinence in children are monosymptomatic nocturnal enuresis (MNE) and overactive bladder (OAB).

9.1. Monosymptomatic nocturnal enuresis

Monosymptomatic nocturnal enuresis (MNE) denotes bedwetting without any other lower urinary tract symptoms (LUTS) and without a previous history of bladder dysfunction. Children with enuresis together with any concomitant LUTS are said to suffer from non-monosymptomatic nocturnal enuresis (NMNE), which is not covered by this guideline.

The occurrence of MNE decreases with age, the prevalence of less than 2 nights a week being around 20% at age 5 and around 8% at age 9 to 10. More frequent MNE is less common. Boys are more often affected than girls.

First line treatment in children with MNE is reassurance, information, behavioural therapy and enuresis alarm.

9.1.1. Clinical trial of a new medicinal product to treat MNE

Only children with frequent symptoms of MNE that affect the quality of life of the child and who do not respond to non-pharmacological treatment, should be included in a study of a new medicinal product. Children participating in a phase II to III clinical trial of a new medicinal product intended for the treatment of MNE should have the diagnosis of MNE made by standard clinical assessments of history taking and physical examination, urinanalysis and completion of a diary recording the frequency of bedwetting. Moreover, information on voided volumes should be measured at baseline. Diagnostic investigations such as ultrasound, urodynamic testing and blood tests are normally not required in an otherwise healthy child with MNE.

9.1.2. Study objectives and clinical outcome measures

The primary aim for developing new drugs for MNE in children should be to obtain improvement during therapy or cure – i.e. dryness after completed therapy. The patient reported outcome should be documented by use of a diary for recording of bedwetting events, which should be completed by the parents. The use of enuresis alarms should be documented.

Episodes of bedwetting based on diaries are considered adequate primary outcome measures in phase II-III studies of children with MNE.

Clinical outcome measures should also include the psychological impact and quality of life of children and their families of treatment. Validated instruments for such measurements should be used.

9.1.3. Inclusion/exclusion criteria

- Diagnosis of MNE should be determined according to ICCS criteria.
- Age at least 6 years
- Patients should preferably be selected at primary care centres
- Patients with MNE should only be included when reassurance, information, behaviour therapy and enuresis alarms have failed to reduce the symptoms.
- For inclusion, the frequency of bedwetting episodes should be at least 3 episodes per week over a 4 week period.
- Patients with symptomatic urinary tract infections should be excluded from the study.

9.1.4. Study design

A new medicine to be investigated to treat MNE should be compared to placebo. As MNE often resolves, the study medication duration for efficacy and safety should be approximately 8 - 12 weeks. Depending on the investigational product, a new medicine to treat MNE could be investigated on an as needed basis. Given that MNE is a benign condition that usually is self limiting, it is critical that a new medicine is shown to be safe.

9.2. Overactive bladder syndrome

The International Children's Continence Society (ICCS) uses the term 'overactive bladder' (OAB) for the clinical condition of urge incontinence and defines OAB as a syndrome affecting the filling phase of the bladder, characterized by symptoms of urgency with or without incontinence. Children with OAB usually have detrusor overactivity at cystometric evaluation. Thus, OAB in children is different from OAB in adults (See 5.2.4). In the following, some aspects on the phase II to III clinical development of medicines for the treatment of OAB urinary incontinence in children are briefly presented.

9.2.1. Etiology and diagnosis

In children, the etiology of OAB is frequently unknown and in these cases the condition is usually referred to as 'idiopathic OAB'. When a known neurological pathology is present, most often neural tube defects, the condition is referred to as 'neurogenic OAB' and is associated with neurogenic detrusor overactivity (NDO). The potential consequences of NDO are more severe and affect the upper urinary tract: Vesicoureteral reflux, hydronephrosis, recurrent pyelonephritis and potentially renal damage. Lower urinary tract symptoms (urgency symptoms) are less common.

In children with idiopathic OAB, the main problem is usually incontinence, which, besides being unpleasant, is a great cause of social embarrassment. The normal development of bladder control varies between children and it is not possible to diagnose idiopathic OAB before the age of 5 years. First line treatment of idiopathic OAB in children is urotherapy, which includes information and behavioural advice. When urotherapy alone does not provide adequate control of symptoms, drug therapy may be considered.

According to ICCS, the diagnosis idiopathic OAB in children is symptom based and consists of history-taking, physical examination and completion of a bladder diary. Uroflow and ultrasound examinations of upper and lower urinary tract are not necessary for the diagnosis but can be used to exclude anatomical changes.

The diagnosis of NDO is based on the documentation of the underlying neurological condition and confirmed by demonstration of detrusor overactivity with urodynamic evaluation.

9.2.2. Selection of patients

Idiopathic OAB and NDO should be studied in separate trials.

Diagnosis of idiopathic OAB should be determined at symptom level. Urodynamic testing is not required for inclusion of children with OAB into phase II or III studies. Children with idiopathic OAB should be included from around age 5 years, when a diagnosis can be reliably established. Although urgency is often a prominent symptom in idiopathic OAB, incontinence should be the inclusion criteria in clinical trials in young children (<11 years), because they are often unable to indicate different bladder sensations (e.g. sensations of urgency, filling). Incontinence may also be the only symptom that is observed by the parents.

Patients with idiopathic OAB should only be included after successful treatment of constipation and when urotherapy, which includes information and behavioural advice, has failed to reduce the symptoms.

In children with NDO, detrusor overactivity as demonstrated by urodynamic evaluation is necessary to establish the baseline. As there is a clinical need to treat children with NDO early, those patients should be included from 6 months of age.

Patients with symptomatic urinary tract infections should be excluded from the studies. A representative distribution of age subgroups should be aimed for.

9.2.3. Study objectives and clinical outcome measures

The primary aim for developing new drugs for idiopathic OAB in children should be to obtain improvement during treatment and/or cure after completion of therapy. The patient reported outcome should be documented by use of a diary for recording of events (micturition and incontinence episodes), which should be completed by the parents for a full week. Measurements of voided volumes should be performed over a period of at least 24 to 48 hours.

The following objective outcome measures are considered adequate in phase II-III studies of children with idiopathic OAB and are based on diaries and measurements:

Change from baseline in

- Mean volume voided per micturition (proposed primary outcome measure)
- Maximum volume voided per micturition
- Mean number of daytime incontinence episodes/24 h.
- Mean number of night-time incontinence episodes/24 h.
- Number of dry (incontinence-free) days/7 days
- Mean number of day-time micturitions/24 h
- Mean number of grade 3 or 4 urgency episodes per 24 hr (in adolescents)
- The presence or absence of post-void residual urine

Moreover, studies should include validated quality of life questionnaires, such as the Incontinence Impact Questionnaire or the Incontinence Symptom Index-Paediatric as secondary outcome measurements.

In children with NDO, the treatment aim should be to maintain a low bladder pressure as assessed by cystometry. The following objective outcome measures are considered adequate in phase II-III studies:

Change from baseline in

- Maximum cystometric capacity (MCC) at leakage or at maximal 135% of age related bladder capacity (proposed primary outcome measure)
- Bladder compliance
- Bladder volume at first overactive detrusor contractions (>15 cm H_2O)
- Number of uninhibited detrusor contractions (> 15 cm H_2O) until leakage or until maximal 135% of age related bladder capacity
- Morning catheterized volume
- Catheterized daytime volume corresponding to functional bladder capacity (at moment that leakage occurs using wetting alarm)
- The presence or absence of post-void residual urine

- Also in children with NDO, studies should include validated quality of life questionnaires as secondary outcome measurements.

9.2.4. Study design

In children with idiopathic OAB, studies should be placebo controlled. In children with NDO, placebo controlled studies, on top of clean intermittent catheterisation, is recommended whenever feasible. In addition, an active comparator is recommended in those age groups where there is an authorized standard medication. An open-label, baseline-controlled study with well defined cystometric endpoints may be acceptable in children with NDO in those age groups where there is no authorized standard medication.

9.3. Dose selection and efficacy studies

Dose finding studies in the paediatric population are generally required. If a dose range has been established in adults, obtaining similar exposure as in adults may be a reasonable starting point. The selection of dose (range) can be based on predictions from models compiled from observed PK and PD data from older children/adults in combination with the known influence of body size and body maturation. Models can also be employed to optimise other design features, e.g. time-points for sampling or number of subjects in various strata. Since frequent sampling in paediatric patients is not feasible for ethical and practical reasons, population modelling is the preferable means of analysing data. For establishing the final dose regimen in children, efficacy and safety studies measuring the clinical endpoint are required. Duration of dose finding phase II studies should be long enough to include the time for reaching maximal effect, a study duration of six weeks being considered the minimum acceptable.

To allow appropriate evaluation of efficacy of an investigational drug in children, a phase III study duration of 3 months is expected for idiopathic OAB as well as for NDO. The evaluation of the primary endpoint should occur when the full treatment effect can be expected to be evident and at the end of the 3 month study period.

9.4. Safety

As treatment for OAB and NDO may continue for long periods, follow-up in children should continue for 12 months in order to demonstrate long-term safety. After the initial 3 months of study, the extension part of the study may be performed as an open label study if appropriate justification can be provided. The safety evaluation of a new investigational drug for the treatment for OAB and NDO in children will depend on the safety profile in adults. Special attention should generally be paid to effects on urinary retention as well as on growth and development.

10. Abbreviations

BOO	Bladder outlet obstruction
BPH	Benign prostate hyperplasia
CBMP	Cell based medicinal product(s)
ICC	Intermittent clean catheterization
ICCS	International Children's Continence Society
ICS	International Continence Society, ICS

IIQ	Incontinence Impact Questionnaire
ITT	Intention to treat
HIFU	High intensity focused ultrasound
HRQL	Health-related quality of life
LPP	Leak point pressure
LUTS	Lower urinary tract symptoms
MCC	Maximum cystometric capacity
MNE	Monosymptomatic nocturnal enuresis
MUI	Mixed urinary incontinence
NDO	Neurogenic detrusor overactivity
NMNE	Non-monosymptomatic nocturnal enuresis
NI	Non-inferiority
OAB	Overactive bladder
PPIUS	Patient's Perception of Intensity of Urgency Scale
Q0L	Quality of life
SUI	Stress urinary incontinence
TEP	Tissue engineered product(s)
UI	Urinary incontinence
UUI	Urge urinary incontinence