27 June 2013

EMA/CHMP/107622/2013

Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on the guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence (CPMP/EWP/18/01/Rev. 1)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Astellas Pharma
2	TMC Pharma Services Ltd on behalf of AltheRx Pharmaceuticals Inc
3	Innovacell Biotechnologie AG
4	Merck Sharp & Dohme (MSD)

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1. General comments

Stakeholder number	General comment	Outcome (if applicable)
1	Astellas welcomes the Agency's efforts in updating the guideline. It is expected that enhanced clarity around the regulatory requirements will facilitate development of new drugs for the treatment of urinary incontinence and OAB. It is perceived that some areas in the current draft guideline could benefit from additional explanation or justification. These have been highlighted in specific comments. In particular, the scientific rationale for some new elements is not indicated, and this makes it difficult to understand what the main aim is for some of the requests e.g. inclusion of subgroups of patients into separate trials. It is understood that the guideline allows for flexibility, and in line with this spirit more precise justification of new requirements would be welcome, to better incorporate new elements into clinical trials or understand when approaches different than the ones recommended are also acceptable.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
112-116	1	Comment: The higher prevalence in women is stated twice. Proposed change: Reword to- 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.	*This has been corrected.*
131-134	1	Comment: For improved readability, lines 122- 124 could be followed by lines 131 to 134. Proposed change: Move paragraph 131-134 to after paragraph 122-124.	*This section has been reworded in line with the proposal.*
135-196	4	Comment: The definition of urgency is missing in this section. Proposed change: Add definition of urgency as the concept is mentioned several times throughout the guidance document.	*Chapter 5 has been rewritten. The definition of urgency is now included in the initial paragraph of this chapter.*
135-196	4	Comment: The definition of nocturia is missing in this section. It should be added to this section.	*The definition of nocturia is now included in the initial paragraph of chapter 5.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Add definition of nocturia in this section as the condition is mentioned several times throughout the guidance document.	
182-184	4	Comment: The recommendation to include urethral pressure monitoring should be removed. Rationale: Urethral pressure profilometry is not standardized and is poorly reproducible, and is not used routinely in clinical practice to diagnose urge incontinence. The recommendation to include an urethral pressure monitoring will put excess burden on investigators and patients with no clear benefit over the presence of detrusor contraction alone or gain of clinically relevant information. The presence of detrusor contraction is widely accepted and should be adequate to demonstrate detrusor overactivity. From ACOG practice bulletin: When are urethral pressure profilometry and leak point pressure measurements useful for evaluation of incontinence? Based on extensive review of the evidence, researchers found that urethral pressure profilometry is not standardized, reproducible, or able to contribute to the differential diagnosis in women with stress incontinence symptoms (22). Therefore, it does not meet the criteria for a useful diagnostic test (22). (There is not even reference to its usefulness in urge incontinence). Proposed change: Remove this sentence or provide references to substantiate the recommendation.	*The recommendation to include urethral pressure monitoring has been removed from section 5.2.*
195-196	4	Comment: The guidance differentiates between OAB and Urge incontinence at the condition level. It is not clear how	*Agreed and changed accordingly.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		urodynamics applies to patients with OAB with urge incontinence since urge incontinence is part of the symptoms of OAB. Proposed change: Add statement on Line 196: Therefore, OAB, *with and without urge incontinence,* cannot be defined at the condition level.	
198-214	3	Innovacell argues that dose finding should primarily be based upon efficacy of IMP by combined endpoints comprising of objective and subjective parameters. Correlation of efficacy with observed urodynamic or structural phenomena is not studied or published and does not necessarily support the identification of a safe and effective dose. As stated in the draft guideline, this type of studies is affected by significant limitations. Standardisation of test procedures and panel rating of test results is recommended but may be insufficient to manage inter-subject variabilities and intra-subject variabilities over time. Also normal values are discussed with no general consensus (ie. max. urethral closure pressure, leak point pressures). However, Innovacell supports the concept of urodynamic and structural studies in concomitance to clinical studies confirming safety and efficacy. Due to practical considerations Innovacell prefers separately organized clinical investigations for urodynamic studies and confirming efficacy and safety.	*As stated in the guideline, urodynamic studies can be useful in early phases of product development. The reasons for this are discussed in section 6.1.* *Method limitations as those listed by Innovacell are well known and therefore section 6.1 lists precautions to take when using urodynamic methods.*
199-203	4	Comment: It is not clear whether this section on urodynamics applies to OAB with and with urge incontinence. Proposed change: Add statement on Line 199: Urodynamic studies may be useful at several stages for product developments for products *for urge, mixed or stress*	*Agreed and changed accordingly.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		incontinence.	
204-206	4	Comment: It is unclear whether Study phase (e.g. Phase I-IIa) requires confirmation of diagnosis for regulatory studies, and for which diagnoses; also unclear what **regulatory studies** means. Rationale: Requiring urodynamics for the confirmation of diagnosis for all regulatory studies, including Phase IIb and Phase III studies, places a large burden on the patient and is not always clinically indicated. For example, straightforward cases of stress or urge incontinence do not necessitate urodynamics in the clinical setting and are most often done by bladder diary alone. In addition, the absence of findings on urodynamics does not necessarily exclude a diagnosis. In a clinical setting, patients may indeed have either stress or incontinence, which can be demonstrated on urodynamics. In addition clarification is needed to what **'regulatory studies'** refer to in this sentence. Proposed change: Add clarification on Line 205- They are hence recommended in addition to history and clinical examination to confirm the diagnosis *of stress, urge, or mixed incontinence,* for the purpose of *early phase* regulatory studies where possible.	*Partly agreed and changed/clarified.*
207-209	4	Comment: Study phases should include a subset of patients. Because clinically meaningful improvements on urodynamics have not been defined, and lack of improvement on urodynamics has not been shown to correlate with lack of clinical response, it seems necessary to indicate in which subset of patients urodynamic studies are considered as supportive parameters in the evaluation of the study outcome.	*Section 6.1 has been reworded, with the aim to further outline when urodynamics can be helpful.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Consider substantiated the proposal with references and clearly indicate the subset of patients where urodynamic studies provide supportive parameters.	
209-210	1	Comment: "In the case of clinical non-responders, urodynamic studies may contribute to failure analysis" may lead to different interpretations, suggest to word as indicated below. Proposed change: Reword to- In the case of clinical non-responders, urodynamic studies may contribute to the understanding of the reasons for lack of response.	*Agreed and changed in line with the proposal.*
219	1	Comment: There is evidence that 4 weeks is a long enough period to observe maximum effects with antimuscarinic treatments and there are indications that this is an appropriate duration for other agents in development (POC/Dose selection). Four-weeks should therefore be the minimum acceptable. If there are specific instances where 6 weeks is considered to be necessary, these should be listed, together with the rationale for a longer observation period. Proposed change: Reword to- ... The duration of phase II studies should be long enough to include the time for reaching maximal effect, a study duration of four weeks is considered the minimum acceptable and several doses should be studied to establish the effective dose. The exception are [list any potential exceptions] where the study duration should be 6 weeks based on [add rationale].	*Partially agreed. The study period should be long enough to include the time reaching maximal effect. A study duration of 6 weeks is the minimum acceptable time for new classes of substances. For classes of substances with well established time to maximal effect, a shorter study period of no less than 4 weeks can be acceptable if adequately justified. The text in section 6.2.1 has been changed in accordance.*
222-224	4	Comment: Given the lower prevalence of men who are medically treated for OAB, it may not be practical to study	*Section 6.2.2 has been updated, now recommending that men and women are*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		men in a separate study. Proposed change: Consider indicating that for OAB, men and women could be studied in separate studies, or the same study with the appropriate inclusion/exclusion criteria.	*analysed separately, with a rationale given for this requirement, but not requiring separate studies for men and women.*
223	1	Comment: The rationale for inclusion of men and women in separate phase II studies is unclear. In line with section 7.1, we propose that men and women could be included in the same phase 2 studies, but data analysed separately. This should facilitate design and results interpretation of subsequent phase III trials. Proposed change: Reword to- ... it is expected that men and women are covered by relevant subgroup analyses (see section 7.1).	*Mainly agreed. Section 6.2.2 has been updated, now recommending that men and women are analysed separately, with a rationale given for this requirement, but not requiring separate studies for men and women.*
223	4	Comment: If men with clinical BPH are excluded from the study, it is not clear why men and women can not participate in the same study.	*The text in section 6.2.2 has been updated.* *As it is difficult to separate prostate-related symptoms in men from pure incontinence, it is preferred that men and women are investigated/analysed separately, unless the pathophysiology of the syndrome/disease is demonstrated to be comparable in men and women.*
225-227	1	Comment: The rationale for inclusion of patients with different symptoms in separate phase II studies is unclear. It is our proposal that, patients with urgency, frequency with or without urgency incontinence could be included in the same phase 2 study and differences evaluated by subgroup analyses as proposed for phase 3 studies (sections 6.3.1 and 7.1).. This should facilitate design and results interpretation of subsequent phase III trials.	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Reword to- ...If a drug is intended both for use in patients with urinary urgency and increased urinary frequency but with no incontinence (the urgency-frequency syndrome without incontinence according to ICS), and for patients with urgency incontinence, patients with incontinence and with no incontinence should be analysed by subgroup analyses.	*Agreed. The text in section 6.2.2 has been updated in line with Astellas proposal.*
225-227	4	Comment: It is unclear whether this applies to the study of OAB patients without incontinence. Additionally, unless the indication for treatment is specific to urgency-frequency syndrome, then OAB patients with and without incontinence could be studied in the same trial with appropriate eligibility criteria. Proposed change: Clearly indicate that if a drug is intended for use in OAB patients with urinary urgency and increased urinary frequency but with no incontinence such patients should be studied separately, or as a stratified subgroup within a larger study with the appropriate eligibility criteria for study participation.	*The text in section 6.2.2 has been updated in line with the proposal.*
228-229	1	Comment: The rationale for inclusion of patients with BPH in separate trials is unclear. It is our proposal that men suffering from BPH on stable treatment for their obstructive symptoms could be studied as part of the general OAB population. Specific information can be obtained from relevant subgroup analysis, as can information be derived from other OAB subtypes. In line with section 7.1, it is understood that men with urinary incontinence associated with BPH are to be included in the same studies, but data analysed by subgroup analysis.	*Not agreed. Urinary incontinence in men with BPH is considered to be distinct from other forms of incontinence. Such patients should be*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Reword to- Urinary incontinence in men with benign prostatic hypertrophy (BPH) may have a different pathophysiology and could be explored by relevant subgroup analyses (see section 7.1).	*analysed separately. The text in section 6.2.2 has been slightly amended on this issue.*
246-256	3	Innovacell states that maintaining a positive pressure difference (Urethral Closure Pressure-Detrusor Pressure) at stress situations is the result of a complex interplay between pelvic floor musculature and external urethral sphincter. The catheterized urethra with concomitant abdominal pressure reading by catheter may not be fully equivalent to the patient's real life situation. Compression of tissues and structure may interfere. Data derived by these methods may be descriptive but suitability for comparative analyses must be expected to be limited. Innovacell considers the Valsalva leakpoint pressure the most suitable urodynamic method to describe the function of the patient's urethral closure mechanism. Innovacell judges video-urodynamic methods less suitable to detect leakage than catheters equipped with conductivity sensors. Innovacell further argues that observation of leakage and reaching negative pressure difference (Urethral Closure Pressure-Detrusor Pressure) may be difficult to correlate, depending on the actual amount of urine leaking, anatomical situation of the patient and the patient's actual cooperation and ability to build and increase abdominal pressure. Abdominal pressure increase may be non-linear. Abdominal pressure increase may be incontinuous.	*It is agreed that maintaining a positive pressure difference at stress situations is the result of a complex interplay.* *The limitation of urodynamic methods in the evaluation of stress incontinence is acknowledged.* *Valsalva leakpoint pressure measurement is one of the methods mentioned in this section.* *The sponsor should give a rationale for the choice of urodynamic methods used in early phase studies.*
263-293	4	Comment: This section is not subdivided into the different conditions covered in the guideline as other sections are.	*There is much overlap between the conditions and a repeated subdivision is not considered*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Based on that clarification of the terminology with regards to OAB is one of the specific areas to be addressed in the revised guideline, for clarity purpose, suggest to consistently subdivide <u>all</u> sections into the different conditions. A good example is Section 5 and its corresponding sub-sections.	*to be necessary.*
266-268	4	Comment: This statement should be referenced.	*Reference: Mostwin, J.L.: Pathophysiology: the varieties of bladder overactivity in Urology 2002; 60:22-26*
272-274	4	Comment: The acceptable grading systems for stress and urge incontinence are not substantiated with examples and references. Proposed change: Recommendation to provide examples and references.	*There are no generally accepted grading scales. Validated grading scales should be used.*
275-276	1	Comment: Same comment as above Proposed change: Reword to- Patients with OAB could also be associated with benign prostate hyperplasia. In that case BPH must be ….	*Not agreed. Patients with BPH are considered to differ from female OAB patients and are therefore to be studied separately. (Section 6.3.1)*
277-278	1	Comment: The rationale for limiting enrolment in clinical trials to patients that have been on stable treatment for BPH for 6 months is unclear. This is not in line with current clinical guidelines on BPH, which for patients with incontinence advise to add another agent, if necessary, after 4 weeks of therapy with either an alpha 1 –adrenoreceptor antagonist or a 5-AR inhibitor.	*Agreed. The time limit for patients to be stable on conservative BPH treatment before inclusion in a clinical trial has been deleted from section 6.3.1.*

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		Proposed change: Reword to- ….and results of the treatment for BPH should have been stable before enrolment, in line with European Clinical Guidelines.	
279-280	4	Comment: Lack of reference to inclusion of elderly patients in Phase III studies. Proposed change: Elderly patients, specified as >65 years of age and >75 years of age, should be included in phase III studies in sufficient numbers to inform on efficacy and safety in the elderly.	*The text in section 6.3.1 has been updated in line with the proposal.*
288-297	3	Innovacell argues that suitable efficacy of an IMP ultimately is confirmed by superiority over a suitable placebo. In urinary incontinence significant sizes of placebo effects, as well as large influences of behavioral components must be expected. Available surgical therapies for stress urinary incontinence are not suitable as comparative treatments in double blind clinical investigations. Double blinded study conduct is impossible when testing against surgical options (ie. Burch colposuspension, TVT). Available surgical therapies for stress urinary incontinence are not standardized but co-exist as large variety of products and procedures. Available surgical therapies for stress urinary incontinence are subject to investigator/surgeon-dependent therapy outcomes that may compose intrinsic biases to clinical investigations built on comparison of IMP with surgical treatment options. Available surgical therapies are not recommended for the entirety of stress urinary incontinent patient population as they are not recommended or approved for females in	*The significant size of placebo effects in the treatment of stress incontinence is acknowledged. Nevertheless, placebo controlled trials have been the standard procedure for new investigational products intended for stress incontinence.* *Also, the limitations of surgical therapies for stress incontinence are well known.*

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		reproductive age or with wish to reproduce. Available surgical therapies may not adequate for patients with fixed urethra due to compromised success ratio and increased incidences of complications/side effects (Haliloglu, Cam; Int Urogynecol J (2010) 21:173–178)	
294	4	Comment: It is unclear if the word "equally" refers to stress incontinence in the preceding paragraph or to placebo. Proposed change: Remove the word ~~equally~~**.**	*Agreed and changed as proposed.*
299-303	4	Comment: The specific guidance for the (co-) primary endpoint(s) is not clear. Additionally how perception of treatment benefit should be incorporated into the objectives and hypothesis structure is unclear as well. Proposed change: Clearly indicate what are considered to be co-primary endpoints in the confirmatory studies and how perception of treatment benefits should be incorporated into objectives and hypothesis of the study protocol.	
299-303	4	Comment: The first part of the paragraph states that patients scoring should constitute the primary endpoint and the last sentence states that at least 2 quantitative symptoms variable should be co-primary. The paragraph which follows also lists examples of quantitative symptoms that are appropriate primary endpoints. Based on the text it is understood that, <u>for all conditions included in the guideline</u>, patient scoring should constitute the primary endpoint in Phase III trials. In addition, at least two quantitative symptom variables are expected to be used as co-primary endpoints. Proposed change: If this understanding is accurate, to avoid	*The initial part of section 6.3.4 has been reworded for clarification. To allow increased flexibility in different situations, two alternative possible study designs are now permitted.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		confusion, refer to co-primary endpoints (line 303 – add an s in endpoints) instead of the singular endpoint. If this is not the case , clearly indicate which should be the primary endpoint(s)- patient's qualitative scoring or at least 2 quantitative symptoms variables	
299-305	1	Comment: The current wording is unclear. The intended meaning of quantitative symptom variables and the distinction from measures of perception of effect is not clear. One possible interpretation is the suggestion of using three (co)primary endpoints, which would have major statistical implications, e.g. multiple testing. The current standard is the use of two clinical endpoints (mainly frequency of micturition and incontinence as recorded by patients) in clinical trials including OAB patients with or without incontinence. For clinical studies in patients with urinary incontinence a single primary endpoint is sufficient. It seems appropriate to always include patient reported outcomes as a key secondary endpoint rather than as a co-primary endpoint. Proposed change: Reword to- The aim for developing new drugs for urinary incontinence should be to obtain improvement or cure of the symptoms for the patient, hence quantitative outcome measures should constitute the primary endpoint(s) in phase III trials. Changes in quantitative symptom measures allow a quantification of changes but cannot serve as surrogate endpoints for perception of effect. It is recommended to use one or two quantitative symptom measures as co-primary endpoints depending on the symptoms of study population, and a patient reported outcome measure as a key secondary endpoint.	*The initial part of section 6.3.4 has been reworded for clarification. To allow increased flexibility in different situations, two alternative possible study designs are now permitted.*
311-312	4	Comment: The proportion of patients requiring surgery is	*It is agreed that patients do not "require" surgery. Nevertheless, the proportion of*

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		not considered to be a clinically informative endpoint Rationale: Surgery for stress incontinence is never "required" and the degree of incontinence may not be the deciding factor. The level of incontinence tolerated by different people is very variable and is influenced by personal perceptions, available support, financial considerations, etc. It can not be standardized. Proposed change: Delete recommendation on lines 311-312.	*patients subsequently undergoing surgery may serve as an informative endpoint and this statement is preserved in paragraph 4 of section 6.3.4.*
336	4	Comment: "The volume of each micturition" as an endpoint is not clear. Proposed change: Consider using either the average volume voided per micturition or maximum volume voided per day.	*In section 6.3.4, this has been changed to "The average volume per micturition".*
345-346	4	Comment: This section states that a diary should and could usually be kept for a complete week; though, a number of OAB products have been approved for market using diaries maintained for as few as 3 days. Proposed change: Consider indicating that a diary including only recording of events (micturition, leakage, urgency and pad use) could be kept for a minimum of 3 days.	*The text on this point in section 6.3.4 has been altered and now states: "A diary including only recording of events (micturition, leakage, urgency and pad use) should and could usually be kept for at least 3 days."*
346-347	4	Comment: The requirement should take into consideration how burdensome this measurement is for patients, and the fact that most OAB approved products have shown reduction in void volume based on 24-48 hour measurements.	*The text in section 6.3.4 is already indicating 24 hours as an absolute minimum for diary recording of events.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: Clearly indicate that a diary including measures of volume should be kept for no less than 24 hours.	
362-365	4	Comment: The intent of this section is not clear. Proposed change: Indicate if this section is meant to capture other quantitative outcome measures that sponsors wish to use which are not explicitly identified under the prior section on quantitative outcome measures?	*This sections deals with the situation that a sponsor may wish to use outcome measures that are not identified earlier in the text.*
376-381	4	Comment: This section is not subdivided by conditions as the other sections of the guidance (eg, Section 6.2), and thus it is not clear if the proposed study duration applies to all patient populations. Proposed change: Recommendation to clearly indicate if considerations about the Phase III study duration applies to all patient populations, including OAB.	*Section 6.3.5 applies to all study populations.* *The lack of specification means that the proposed study duration applies to all patient populations.*
377–378	2	Comment: The proposed text states that “To allow appropriate evaluation of both safety and efficacy of an investigational drug, a study duration of at least 6 months is expected”. No explanation or justification of this change from the previous guideline in study duration is given. A PubMed search reveals 9 clinical efficacy studies of drugs published in the last year – none of these had a duration greater than 12 weeks. Similarly, on review of the published literature we can find no body of evidence to suggest that expert opinion is moving towards a need for 6 month efficacy studies.	*After consideration of several comments to this draft guideline, and after consultation with other guidelines in urology, the text has been changed on this point.* *The new text states “To allow appropriate evaluation of efficacy of an investigational drug, a study duration of at least 3 months is expected. However, for demonstration of maintenance of treatment effect a longer study period should be considered.”*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		The European Association of Urology "Guidelines on Urinary Incontinence", published in 2012, includes a grade "A" recommendation for antimuscarinic drugs based on grade "1a" evidence; inspection of the evidence cited shows that none of the studies involved a treatment period of more than 12 weeks. This suggests that current expert opinion views 12 week studies as being appropriate to demonstrate efficacy in incontinence. This view is further supported by our consultation with seven prominent opinion leaders (names to be provided on request) whose opinion was that there is little change in efficacy after 12 weeks. Further arguments against the adoption of a 6-month study duration would be (i) the ethical issues in randomizing patients to placebo for this period and (ii) the probable high drop-out rates that would make sample size calculations problematic. The issue of safety is already dealt with in ICH E1 and this is reflected in lines 379-381. Proposed change: We therefore suggest that the sentence be changed to: "To allow appropriate evaluation of efficacy of an investigational drug, a study duration of at least 3 months is expected". This would be consistent with the current regulatory guidance.	*On safety, the new text states "To provide an adequate safety database, a further follow up is necessary so that the total study duration is at least 12 months; this may be performed as an open label design if appropriate justification can be provided."*
377-379	4	Comment: This section states that a 6-month study duration is expected to allow appropriate evaluation of both safety and efficacy of an investigational drug, but products thus far approved for overactive bladder have been based on 3-	*Section 6.3.5 has been reworded. The new wording says that for efficacy at least 3 months study duration is expected while for safety 12 months data is expected.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		month efficacy data as per currently approved CHMP guidance. It is necessary to clarify if this 6-month period for collection of efficacy data applies to overactive bladder drugs, as the rationale is not clear. Proposed change: Indicate the rationale to depart from the previous guidance.	
377-381	1	Comment: The scientific rationale supporting expected full treatment effect after 6 months in adults is unclear. Maximum treatment effect vs baseline can be seen within 3 months with current available treatments. No trials have been identified where the efficacy of urinary incontinence drugs was found to be incomplete and/or not of maximum magnitude versus baseline after 3 months of treatment. Most studies have demonstrated the difference between the investigational drug and placebo to be at its maximum from 4 weeks onwards. In addition, exposing patients for 6 months to placebo, when marketed products exist, would be unethical in the absence of a strong scientific rationale. Furthermore, there is no historical precedent of assessments at 6 months, which would make comparisons with historical data impossible, as the body of evidence collected so far is based on assessments after 3 months of treatment. This considerably longer trial duration may have a negative impact on patient withdrawal rates and, in combination with the burden imposed by the trial's assessments, is also likely to adversely affect patient willingness to participate in trials. Proposed change: Reword to- To allow appropriate evaluation of both safety and efficacy of an investigational drug, a study duration of at least 3 months (appropriate to the mechanism of action of the investigational product) is expected. To provide an adequate safety	*Partly agreed. Section 6.3.5 has been reworded. The new wording says that for efficacy at least 3 months study duration is expected while for safety 12 months data is expected.*

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		database, follow up for a year is necessary; this may be performed as an open label design if appropriate justification can be provided.	
390-392	4	Comment: This section states that drugs intended for use in urinary incontinence may affect bladder emptying, and it is important to monitor patients for increased residual urine and urinary tract infections apart from general adverse event monitoring. Proposed change: Clarify what is meant by this statement in the context of 'apart from general adverse event monitoring'.	*The wording of section 6.3.6 has been modified, to further elucidate what kind of adverse events that should be especially monitored.*
410-411	1	Comment: Please clarify that responder analysis is a secondary analysis since dichotomizing a continuous parameter will result in loss of information and power. Proposed change: Reword to- ... A responder analysis should be performed as a secondary analysis....	*The clarification requested in section 7.1 has been provided.*
410-413	4	Comment: It should be noted that clinically relevant cut-off estimated from empirical data can vary from study to study, population to population and for different products. It is difficult therefore, if not impossible, to specify a single cutoff for an entire program. Proposed change: Consider changing the sentence accordingly 'A clinically relevant cut-off for the proposed primary endpoint ~~has to~~ *is suggested* to be defined *as possible*.	*The text of the second paragraph of section 7.1 has been modified, for clarification.*
466-476	3	In addition to comments on item 6.1. Innovacell argues that the sensitivity of established methods to assess structural	*Principally agreed.*

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		findings ie. muscle dimension or volumes may be insufficient to assess pre-post changes correlated with regeneration of rhabdosphincter function by TEP. As per current literature anatomical normal values for structural parameters vary over wide ranges and seem not correlated with pathology. It is unclear, whether clinically relevant effects of TEPs can be observed by structural parameters e.g. rhabdosphincter's volume or thickness. Innovacell argues that subtle changes in anatomy may affect the stress continence system. (Morgan, DeLancey; J Urol. 2009 July; 182(1): 203–209. doi:10.1016/j.juro.2009.02.129.) Innovacell states that effects on contractility of urethral sphincter muscle may be difficult to observe and evaluate. Inter-subject variability seems to be much larger than phenomena observed. It must be expected, that pre-post differences in contractility cannot be correlated with clinically relevant effect sizes of TEPs. (Umek, Hanzal; American College of Obstetricians and Gynecologists VOL. 100, NO. 4, OCTOBER 2002 0029-7844/02-2002) Innovacell argues that findings related to integration of newly formed tissue into surrounding muscle tissue is subject to practical limitations when tested in humans. Suitable animal models may offer advantages for assessment and orthogonal analysis of findings.	*The wording in this section has been modified.*
486-487	3	For TEPs in SUI the superiority against standard of care is requested. Innovacell argues that the standard of care in SUI is not standardized and with respect to surgical treatment options does not apply to the entirety of patients suffering from SUI that may be suitable for tissue engineering therapy (see comments on item 6.3.3.). Innovacell argues that the draft guideline is inconsistent as 6.3.3. requests placebo controlled trials and 8.3.3. explicitly	*As in many other areas, standard of care may have local variations. Nevertheless, standard of care can be a relevant comparator for TEPs in SUI, where and placebo controlled trials are not feasible and surgery can not be used as comparator.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		requests comparison while standard of care for TEPs in SUI. Innovacell's opinion is, that comparative testing in SUI must always be combined with double-blind trial design, therefore placebo control should be the clinical trial conception of choice to determine efficacy of TEPs.	