EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 October 2015
EMA/CHMP/684234/2015
Committee for Medicinal Products for Human Use (CHMP)

# Overview of comments received on 'Note for guidance on clinical investigation of medicinal products for treatment of asthma' (CHMP/EWP/2922/01/rev.1)

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

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 01 | Swissmedic, Swiss Agency for Therapeutic Products |
| 02 | Professor Paula Williamson, University of Liverpool, on behalf of the COMET Initiative Management Group |
| 03 | Comet Initiative Management Group – paediatric |
| 04 | Dr. Roberto Frontini, pharmacist. Universitätsklinikum Leipzig, Leipzig, Germany |
| 05 | Quintiles |
| 06 | Cytos Biotechnology, Wagistrasse 25, CH-8952 Schlieren, Zürich, Switzerland |
| 07 | Swiss Biotech Association |
| 08 | EFPIA - Pär Tellner (par.tellner@efpia.eu) |
| 09 | EPAG |
| 10 | Group of French Experts:<br>Pr Pascal Demoly, Pulmonologist, CHRU Montpellier, France<br>Pr Philippe Devillier, Pulmonologist, Foch Hospital, Suresnes, France<br>Pr Alain Didier, Pulmonologist, Larrey Hospital, CHU, Toulouse, France<br>Pr Arnaud Bourdin, Pulmonologist, CHRU Montpellier, France |
| 11 | Faculty of Pharmaceutical Medicine |
| 12 | Allergopharma GmbH & Co. KG, Clinical Trial Department, Reinbek, Germany |
| 13 | Teva Pharmaceuticals Ltd |
| 14 | STALLERGENES, 6 rue Alexis de Tocqueville 92160 Antony, France |
| 15 | ALK-Abello A/S, Bøge Alle 6, 2970 Hørsholm, Denmark |
| 16 | EAACI |
| 17 | Medicines Evaluation Board, Netherlands |
| 18 | PPD Inc. |
| 19 | EAMG European Allergen Manufacturers Group |

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| Stakeholder no. | Name of organisation or individual |
|---|---|
| 20 | Science Pharma, Poland |
| 21 | Mylan |

# 1. General comments – overview

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
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| 05 | Quintiles appreciates EMA's consideration of our suggested clarifications and revisions for inclusion in the final Note for Guidance. Please do not hesitate to contact us to further discuss the specific comments provided below. | |
| 06 | Cytos thanks the European Medicines Agency (EMA) for the opportunity to provide comments on the "Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Asthma, draft' (CHMP/EWP/2922/01 Rev 1, 27 June 2013)". Immune modulators are a new class of asthma controller medications which are currently in development. Cytos recommends that these new controller medications are reflected in the clinical asthma guideline in a distinct group within the controller medications as they do not necessarily fit into the currently proposed categories (sections *1. Introduction*, *4.3.4.1 Design*). In the final guideline. Cytos regards it as important to provide specific guidance to design the clinical development plans/studies for the immune modulators.<br>Cytos is a public biopharmaceutical company focused on the development of targeted immunotherapies. The Company's lead product candidate CYT003-QbG10 (CYT003) is a novel, first-in-class, immune modulator in Phase 2b clinical development as a potential new treatment for asthma.<br><br>Deletions are shown as strikethrough: ~~deleted~~ | Guideline revised to not exclude those treatments. |

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
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| | Additions are shown in bold, italic, underlined: ***new*** | |
| 08 | EFPIA welcome the release of the revised Note for Guidance (NfG) on clinical investigation of medicinal products for treatment of asthma' and more specifically the addition of a dedicated chapter on developing asthma medicines in children. It is a sound, comprehensive document providing guidance on the clinical development in asthma that is reflecting current understanding of diagnosis, treatment and clinical assessment methods of asthma. However, we have the following major issues:<br><br>1. **Including patients in pharmacodynamics studies:** there was a specific statement in the initial NfG (page 3 of the 2002 NfG) which was providing useful information and is no longer included in this revised NfG. Such a reference would be useful to be kept in the revised NfG since patients are often included in these studies provided their asthma is well controlled. It would be useful mention in the revised NfG that 'PD studies may be required and these should be double blind and placebo controlled. They may involve patients and healthy volunteers although the effect on asthma severity on the distribution, and hence pharmacodynamics, of inhaled drugs may limit the interpretation of data from non-asthmatic subjects'.<br><br>2. **Clinical development:** with reference to lines 174/175, we are concerned that the expectation for separate studies in patients with different degrees of severity of asthma would not be appropriate for all new drugs being developed for asthma. We | 1) Accepted<br><br>2) Partially accepted. It is not mandatory to test the effect of the drug in every degree of asthma severity; this will depend on the type of MP. But given the differences in background therapy and the comparator of choice depending on the asthma severity, studies should be conducted separately for each subset of patients. Current wording allows for such flexibility but the text has been slightly revised.<br><br>3) Accepted. Text revised accordingly<br><br>4) Partially accepted. Text revised. Extrapolation could be considered acceptable in children above 6 years upon adequate justification. It is recommended to discuss this possibility at SAWP on a case by case basis. For new medicinal products or products with a novel mechanism of action, a full development program is expected. Concerning study duration, the comment is accepted and flexibility has been introduced.<br><br>5) Accepted. |

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| | believe that sponsors should be allowed and encouraged to develop drugs with indications limited to specific severity categories (e.g. patients with GINA 4-5 asthma who are not controlled on current therapy) and that the guideline should clearly reflect that in this case efficacy testing would be required in this specific severity category only.<br><br>3. **Clinical endpoints:** Per reference with lines 422/422, we question the use of improvement in lung function and reduction in exacerbations as co-primary endpoints in clinical trials of new asthma controller medications. Clinical trials of new biologics e.g. omalizumab, mepolizumab and others show that reduction in exacerbations and improvement in symptoms can occur without a large change in lung function. It is recommended that Lung function and reduction in exacerbations should be separate endpoints and their relative weight (primary *vs*. secondary) should depend on the objectives of each particular trial.<br><br>4. **Clinical development in children:** We are concerned that the new paediatric section in the revised NfG will require that full and burdensome development programs be undertaken for new products for asthma in children. We are concerned that there is no discussion included within the NfG to consider the role of pharmacometrics (including modelling and simulation techniques) for pragmatic trial design, or whether pharmaceutical development of paediatric therapeutics is appropriate for all mechanisms of action or pharmaceutical forms. While we | |

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| | acknowledge that extrapolation from adolescent/adult data to children less than 6 may not be appropriate in all cases, the recommendations contained within the NfG, do not seem to take into consideration the practical applications of extrapolation for data generation in children aged 6-11. Since extrapolation depends on a series of evidence-based assumptions, including the similarity of disease/progression and response to intervention in the adult and paediatric populations, identification of biomarkers that could be utilized to demonstrate a similar exposure-response between the adult/adolescent and child populations may enhance and make more efficient the drug development process, by allowing for clinical trial simulations. In doing so, opportunities for introducing innovative trial designs (e.g., smaller trial samples) to then validate those simulations might be possible. This is increasingly important as every product in development has commitments to conduct research in agreement with a paediatric investigation plan, where the competitive environment for the available subjects has increased.<br><br>With reference to lines 614-618, we are also concerned that a requirement for 1 year placebo-controlled trials for children < 6 would expose children to unnecessary risks when comparator drugs are available. The clinical trial design should be appropriate for the drug that is being developed, keeping in mind the safety of the participants in the trial. Flexibility in using comparator drugs in trials of shorter duration would be preferable, depending on the indication. In some cases, a 6 | |

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| | month trial during the winter months might be appropriate for assessing reduction in exacerbations. This approach would limit potential risks for patients in placebo or comparator groups (refer to EMA/726030/2012, page7). The clinical trial design should be flexible and should be discussed in advance with the appropriate Health Authorities.<br><br>5. **Immunotherapy:** Distinction should be provided between "specific immunotherapy" relating to allergen products, and biological treatments (e.g. monoclonal antibodies) that also constitute a specific form of immunotherapy, but with known, asthma-related mechanism of action. See specific changes for individual line numbers as offered. Also, propose differentiating between "allergen-specific immunotherapies" and "biologic immunotherapies".<br><br>In addition, EFPIA have specific comments on the text which are displayed in the following pages. | |
| 10 | It could be appropriate to replace "Specific Immunotherapy" by "Allergen Immunotherapy", which is more appropriate and more "specific" of the allergy field (Calderon et al. Allergy 68 (2013) 825 – 828 | Accepted |
| 13 | We welcome this guidance and the effort to update older guidelines that have become dated and give fairly specific thinking on comparative assessment requirements.<br>We would like to address that specific population evaluation requirements would be of value, as no guidance is given on | The guideline does not exclude those patients but specific guidance is not included due to limited regulatory experience. See text lines 169-171, 204-5, 209-10 |

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| | development requirements for therapeutics targeted toward specific subpopulations (i.e. eosinophilic asthma, atopic asthma, etc.). | |
| 15 | Specific and allergen-specific immunotherapy should be replaced with allergy immunotherapy. The arguments for moving to the terminology is explained in the PRACTALL consensus report (J Allergy Clin Immunol, 2013, 131:1288-1296) | Accepted |
| 17 | This document is a revision of the earlier Note for Guidance of 2003 (CPMP/EWP/2922/01). The treatment of asthma has been evaluated in the meantime. The current revision has taken into account the updated international clinical recommendations in the treatment of asthma. Especially the recommendations for the investigations in children are welcomed. | No action needed. |
| 18 | In several sections emphasis is placed on the importance of including current standard of care control arms for both first-line and add-on treatments in development. It is implied that placebo comparisons are appropriate as the primary comparisons; hence these will drive study power calculations. In this case the active treatment arm will be a benchmark to review safety and efficacy data rather than for formal efficacy comparisons: studies are very unlikely to be powered for such comparisons.<br>It would be useful for the Agency to clarify what's the intended analysis for the comparison between the two actives. | Accepted. Text clarified. |
| 20 | It would be useful to have clear definitions of "*controlled, partly controlled and uncontrolled asthma*" included in the guideline, either in the Introduction, where the new asthma classification is described, or in Definitions. The table describing clinical characteristics of the three asthma stages, e.g., as presented in *GINA Pocket Guide for* | Accepted. Previous definitions were in line with GINA 2012. GINA guideline has been recently updated. Current classification/definitions included. |

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| | *Asthma Management and Prevention,* could be considered. | |
| 20 | According to the proposed guideline, exploratory and pivotal efficacy and safety studies should be placebo-controlled. We would like to ask the Agency for a rationale behind the recommended study design, especially taking into account ethical aspects and patients' safety. In our opinion, keeping asthma patients (children in particular) on placebo for several weeks/months is (to say the least) questionable from ethical point of view, even if the shortened length of study-participation is allowed. | Text clarified. Placebo controlled studies are only allowed in mild patients or in add-on studies for the more severe population. See lines 381-4 |
| 21 | Mylan welcomes this revision of the CHMP note for Guidance on the Clinical Investigation of Medicinal Products for Treatment of Asthma, taking into account the most recent Global Initiative for Asthma (GINA) proposals for the classification and treatment of asthma. These changes will be beneficial to companies involved in the development of medicinal products for the treatment of asthma. Whilst we welcome reference to global GINA classification, it would be beneficial if the interpretation of asthma definitions were consistent throughout the document and have therefore proposed some specific amendments in line with these inconsistencies.<br><br>We would also like to understand the basis for some of the clinical proposals made, such as recommended study durations, which do not appear to correlate with the pharmacology of some of the drugs that might be involved, or FDA guidance. These clinical proposals could prove to be a hindrance to global development programmes. | Accepted. Text revised.<br><br>Comment accepted and text revised to allow more flexibility. |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| 74-77 | 01 | Comments:<br>Asthma is not only one disease regarding mechanism and treatment. Thus we would propose emphasizing heterogeneity<br><br>Proposed change (if any):<br>It is a syndrome composed of heterogeneous diseases regarding mechanisms, manifestations and also its response to treatment | Not accepted given that no relevant guidelines refer to this condition as such, but the existence of different phenotypes is emphasised. |
| 175-176 | 01 | Comments:<br>Response to treatment may not only depend on severity but also on type of asthma<br><br>Proposed change (if any):<br>… studies are carried out for each grade of asthma severity and each of the various asthma-types which the new product … | Partially accepted. No specific guidance on studies in phenotypes given the limited regulatory experience. |
| 259-261 | 01 | Comments:<br>It could be helpful to characterize additionally also the population of exacerbations studies.<br><br>Proposed change (if any):<br>The studies should be performed in 'enriched' populations at risk (e.g. in patients with history of | Accepted |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | frequent severe exacerbations). | |
| 324 | 01 | Comments:<br>To include a placebo control is not an 'alternative 'possibility to characterize the dose response curve.<br><br>Proposed change (if any):<br>Canceling the word "Alternatively". | Accepted |
| Lines 586-605 | 02 | Comments:<br>There is increasing recognition of the value of core outcome sets as a means of improving the efficiency of evaluations of the effects of interventions across health and social care. The COMET Initiative is facilitating this work, in part by the identification of core outcome sets that have already been developed (www.cometinitiative.org). COMET has identified three studies with the aim of developing a core outcome set for trials in children with asthma (1,2,3). Core outcome sets do not need to comprise an extensive list of all outcomes that might be measured in research. Rather, a few particularly important outcomes are identified which reflect the ways in which patients, families, and clinicians assess whether a treatment regime is satisfactory, and make shared decisions about whether to continue or modify it. The three studies involved different stakeholder groups, and used different methodological approaches (summarised below), but the resulting core outcome | Accepted. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | sets included two common outcomes (see table below).<br>**Sinha et al:** UK paediatricians, specialist nurses, parents and young people with asthma participated. Outcomes for pre-school (younger than 5 years) and school-aged (at least 5 years but not yet 18) children were considered separately. Outcomes measured in clinical trials were identified by a systematic review and from open questioning. Results from parents and clinicians were generally concordant, but parents placed more emphasis on long-term treatment effects. Although lung function is frequently assessed in asthma clinical trials because it is an objective evaluation of efficacy, this study found that parents and clinicians place much more emphasis on clinical measures of asthma control when assessing the effectiveness of therapy. Similar outcomes to those identified for this core outcome set were also found to be important in the Dutch evidence-based guideline for paediatric asthma management (Nicole Boluyt, personal communication).<br><br>**Reddel et al:** The American Thoracic Society (ATS) and European Respiratory Society (ERS) held workshops, attended by 24 clinical researchers, with the aim of recommending outcomes to select in clinical trials of regular therapies for asthma, and how these | |

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| | | could be measured in a standardised manner. These recommendations relate to adults and adolescents, but the authors suggest that, with some special considerations, the outcomes could also be relevant for children older than 6 years. Outcomes measured in clinical trials were identified by a literature review. Working groups comprising clinicians, researchers, and pharmaceutical industry representatives, reached consensus, in round-table open discussions, about the suitability of these outcomes for evaluating current and future asthma-related problems. Two paediatricians assessed whether the recommendations were applicable to clinical trials in children.<br><br>**Busse et al:** National Institutes of Health (NIH) institutes and the Agency for Healthcare Research and Quality convened a workshop involving 7 expert subcommittees to propose which asthma outcomes should be assessed with standardized methodology in future asthma clinical research studies. Each subcommittee used comprehensive literature reviews and expert opinion to compile a list of asthma outcomes and classified them as either core (required in future studies), supplemental (to be used according to study aims and standardized), or emerging (requiring validation and standardization). This work was discussed at an NIH-organized workshop in March | |

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| | | 2010 and finalized in September 2011. The Planning Committee ensured that each subcommittee had representatives from the specialties of adult asthma, paediatric asthma, pulmonology, and allergy/immunology. Furthermore, representatives from the fields of pharmacology, biostatistics, primary care, and behavioural/social science were included in the subcommittee membership.<br>**References**<br><br>1. Busse WW, Morgan WJ, Taggart V, Togias A. (2012) Asthma outcomes workshop: overview. Journal of Allergy and Clinical Immunology, S1-S8<br><br>2. Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. (2009) An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. American journal of respiratory and critical care medicine, 180(1):59<br><br>3. Sinha IP, Gallagher R, Williamson PR and Smyth RL. (2012) Development of a core outcome set for clinical trials in childhood asthma: a survey of clinicians, parents, and young people. Trials, 13:103 | |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | Proposed change (if any):<br><br>(1) There should be recognition of these 3 studies and their common findings in the guidance document.<br><br>(2) Lung function is frequently assessed in asthma clinical trials because it is an objective evaluation of efficacy, but the primary outcomes when assessing the effectiveness of therapy should be outcome measures that have been found to be important to patients and those who care for them.<br><br>(3) A core outcome set for childhood asthma, that suits the needs of researchers and improves the usefulness of clinical trials to clinicians, parents, and policy-makers, can be based on the common findings of these 3 studies, namely that symptoms and exacerbations should always be measured in trials in children with asthma. Agreement amongst a wider group of people involved in such trials should focus on identifying the best ways to measure symptoms, and standardising the definition of an exacerbation. Greater emphasis should be placed on reporting these outcomes separately rather than in composite scores.<br><br>(4) Further discussion should also address the value of including outcomes that were identified by at least 2 of | |

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| | | the 3 studies: quality of life, activities, reliever use and physiological measures of lung function, and whether outcomes reflecting long-term beneficial and harmful effects of treatments should be measured in all trials recruiting children with asthma.<br><br>(5) Finally, treatment side effects and death should always be reported in clinical trials in children with asthma. | |
| 249-251 | 04 | Comments:<br>While from a medical point of view the need of systemic corticosteroids has to be considered equivalent to emergency visit or hospitalisation, from the perspective of patients (and payers) is not. Thus a differentiation of the exacerbations in “severe” and “requiring hospitalisation” may be useful. | Partially accepted. The guideline allows the use of generally accepted definitions for exacerbations. |
| 154 - 155 | 05 | Comments:<br>We appreciate EMA’s recognition of the difficulty in demonstrating 12 – 15% reversibility of FEV1 in patients on controller therapy, and the flexibility to rely on patient medical history to meet the reversibility criteria. We would point out, however, that older patients can present with mixed disease having both COPD and asthma components. We therefore recommend that for patients over 40 years of age, the reversibility criterion should have been met within the two years preceding enrolment, so as to avoid | Partially accepted. Text revised according to GINA guideline and also in consistency to COPD EU regulatory guideline. See Section 4.1 |

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| | | enrolling patients who have predominantly COPD disease, as these patients would be expected to be less responsive to therapy.<br>Proposed change (if any):<br>Addition of the sentence: "For patients over 40 years of age, the reversibility criteria should have been met within the two years prior to enrolment, so as to avoid enrolment of patients with mixed disease having a significant COPD component, as these patients would be expected to be less responsive to therapy" after "...provided by the patient's medical history". | |
| 296 | 05 | Comments:<br>Eosinophil counts are mentioned as a biomarker of airway inflammation, but it is not specified whether eosinophils are to be measured in blood and/or sputum. Recent research supports the use of sputum sampling as a valuable research tool (Clin Exp Allergy 2012; 42:650–658.; J Allergy Clin Immunol 2011; 127:355–360); therefore, we advocate acceptability of both blood and sputum sampling.<br><br>Proposed change (if any):<br>Addition of italicized text, "Eosinophil counts *measured in blood or sputum* and fractional concentration of..." | Text revised. Need to use validated methods |
| 610 - 613 | 05 | Comments:<br>In the section describing trial design for studies in | Accepted. Text revised to make it clear that it is the severity of asthma what drives the accepted comparators. |

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| | | children 6 years of age and older, the first sentence states that “3-arm studies (study drug – placebo – active comparator (standard of care) are preferable,” whereas the second sentence states that “New biological treatments should be studied in comparative trials, demonstrating superiority over standard treatment or as add-on to standard treatment in those patients uncontrolled on low-dose ICS.” Assuming that the rationale for the latter sentence is that biological treatments have been traditionally reserved for severe asthmatics, in whom use of placebo would not be appropriate, we suggest adding this information so that the different approach taken with biological treatments can be directly understood by the reader. Addition of this rationale will also indicate that were a biological treatment to be developed for treatment of less severe disease, a 3-arm study may be appropriate.<br><br>Proposed change (if any):<br>Addition of italicized text, “…3-arm studies (study drug – placebo – active comparator (standard of care) are preferable *for non-biological treatments*. *Because biological treatments are recommended for treatment of severe asthmatics, in whom use of placebo would not be appropriate, n*ew biological treatments should be studied in comparative trials, demonstrating | |

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| | | superiority over standard treatment or as add-on to standard treatment in those patients uncontrolled on low-dose ICS." | |
| 662 - 663 | 05 | Comments:<br>While the desirability of including dose counters on inhaler devices intended for use by the paediatric population is self-evident, doing so will pose blinding issues when comparing to standard marketed products. We request that EMA comment in the guidance on how this issue should be addressed.<br><br>Proposed change (if any): | Specific Section on considerations for use of devices in the paediatric population has been added. |
| Section 4.1 Selection of patients Lines 206-207 | 06 | Comments:<br>Sub-populations may not always be identified a priori, particularly for immune modulators. Therefore Cytos proposes to modify the language and include the need to specify sub-populations a priori if the data are intended to be used in the SmpC (summary of product characteristics).<br><br>Proposed change (if any):<br>Relevant identified sub-populations should be justified and defined a piori in the study protocol ***if intended to be included in the product label.*** | Not accepted. Relevant subpopulations should be identified a priori based on preliminary studies, independently on whether these will finally be included in the SPC. This will depend on its relevance for prescribers. |
| Section 4.2 Method to assess | 06 | Comments:<br>Immune modulators should be reflected within this section. Therefore, CYTOS recommends to update the | Accepted. However, text has been revised in the Confirmatory trials Section 4.3.4.4) as it is more appropriate |

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| efficacy Lines 216-218 | | guideline as follows:<br><br>Proposed change (if any):<br>Lung Function: Both FEV and PEF reflect airway obstruction and are accepted as spirometric evaluations of the effect of anti-asthma drugs. Pre-bronchodilator FEV1 is considered the most suitable variable ***for asthma treatments where it is considered appropriate and*** has been considered as a measure of asthma control as it is influenced by short-term fluctuations in airflow limitation. | |
| Section 4.2 Method to assess efficacy Lines 223-224 | 06 | Comments:<br>Immune modulators should be taken into consideration, Therefore, CYTOS recommends to update the guideline as shown below<br><br>Proposed change (if any):<br>The timing of the measurement of lung function should be standardised ***where applicable to the treatment schedule*** and recorded in relation to the last dose of the test drug and concomitant medication. | Not accepted. Its self-evident |
| 4.2. Method to assess efficacy Lines 244-258 | 06 | Comments:<br>Asthma is a variable disease where treatment is adjusted on the basis of loss of asthma control. Loss of control is indicated by a worsening of symptoms or the development of an exacerbation. This guidance should outline for the purposes of clinical trials and label | Accepted. The use of definitions according to relevant guidelines is clearly reflected. However, a general requirement to only target severe exacerbations is not considered appropriate, and should be justified on a case by case basis. |

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| | | claims, the definition for an asthma exacerbation that should be applied in clinical trials.<br><br>This Guidance is in alignment with the ATS/ERS definitions of asthma exacerbations:<br><br>Mild: The Task Force offers no definition of mild asthma exacerbations, as these cannot be distinguished from transient loss of asthma control.<br><br>Moderate: deterioration in asthma symptoms and/or lung function with an increase use of rescue bronchodilator lasting for 2 days or more but does require systemic corticosteroid use.<br><br>Severe: requires the use of systemic corticosteroids for at least 3 days. Two courses of systemic corticosteroids separated by at least 1 week are regarded as a separate exacerbation.<br><br>We acknowledge that there are advantages of standardised definitions, however guidance should be provided for the use in clinical trials and be useful for inclusion into the SmPC. Therefore, only the definition of a severe exacerbation should be used for evaluation as an endpoint in clinical trials. | |

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| | | Proposed change (if any):<br>Asthma Exacerbations:<br>Exacerbation rate is a clinically relevant endpoint to assess controller treatment in asthma patients. The prevalence of asthma exacerbations is identified in clinical guidelines as an important component in the achievement of asthma control. The definition of exacerbation and the severity of the exacerbation should be pre-defined in the study protocol. The following definitions for exacerbations should be considered:<br><br>Severe exacerbations of asthma are ~~usually~~ defined as a requirement for systemic corticosteroids or an increase from the maintenance dose of ***oral*** corticosteroids for at least three days and/or a need for an emergency visit, or hospitalization due to asthma. ***Two courses of systemic corticosteroids separated by at least 1 week are regarded as a separate exacerbation.***<br><br>***The definition of a severe exacerbation should be used for evaluation as an endpoint in clinical trials.*** | |
| 4.2. Method to assess efficacy | 06 | Comments:<br>The patient inclusion criteria for an exacerbation endpoint, if selected appropriately could allow for 6 | Accepted. Text clarified to allow flexibility where justified according to the population/MoA |

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| Lines 259-264 | | month duration for the study. This effect can be demonstrated irrespective of seasonal variation. Seasonal variation is important in specific immunotherapy targeting seasonal allergens.<br><br>Proposed change (if any):<br>The methods used to capture (as percentage of patients, annualized rate, time to event) and analyse this endpoint should be justified as should the change in the number of exacerbations thought to be clinically relevant. The length of the study should be of sufficient duration to capture these events (**at least 6 months** ~~at least 12 months~~) and ***include*** ~~as recruitment should continue throughout all four seasons~~ a twelve-month follow-up ***if applicable*** ~~is a minimum requirement~~. | |
| 4.3.1. Pharmacodynamic studies Lines 308 - 312 | 06 | Comments:<br>Likewise, pharmacodynamics studies are not possible for general immune modulators which may exert their effects by inducing subtle changes which cannot be measured systemically. Measures as described below for specific immunotherapy may not be possible for immune modulators.<br><br>Proposed change (if any):<br>Formal pharmacodynamic studies are not possible for allergen products ***or certain immune modulators***. | Accepted. |

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| | | However, to show the effect of specific immunotherapy on the immune system immunological changes (e.g. changes in allergen specific IgG levels, T-cell responses, and/or cytokine production) and/or modifications of organ specific response (e.g. provocation tests) should be measured***, if possible***. These parameters can be followed in other studies on specific immunotherapy. | |
| 4.3.2. Pharmacokinetic Studies Lines 317 - 319 | 06 | Comments:<br>Some drugs, such as immune modulators, may be given in small doses infrequently compared to usual dose regimens of small molecular drugs. Therefore, conventional pharmacokinetic parameters cannot be applied. CYTOS proposes to modify the wording to reflect products which cannot be characterized by ADME.<br><br>Proposed change (if any):<br>Pharmacokinetic studies are not possible for products for specific immunotherapy ***or certain immune modulators***. During specific immunotherapy ***or treatment with certain immune modulators which are given at low doses and infrequently***, usually plasma concentrations of the active substance are not measurable, due to the nature of the product. | Partially accepted. Text revised. |
| 4.3.4.1. Design | 06 | Comments:<br>Cytos acknowledges that immune modulators belong | Not accepted. In general terms, 12 weeks is not considered sufficient to demonstrate efficacy/safety for a controller |

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| Lines 355-360 | | to the controller medications. CYTOS however notes that no specific guidance is given on immune modulators and recommends providing a new paragraph within the controller medication section reflecting the clinical design recommendation for an immune modulator. Efficacy for controller medication can be demonstrated after 12 weeks; hence a primary endpoint after 3 months is sufficient.<br><br>Proposed change (if any):<br>Controller medication<br>Claims for chronic treatment with controller medication should be supported by the results from randomised, double blind, parallel group, controlled clinical trials of at least three months duration, although a longer duration may be necessary depending on the endpoint selected (for example, exacerbations). The established use of inhaled corticosteroids as first choice controller treatment for most patients makes these drugs the comparator of choice.<br><br>***Immune modulators***<br>***The primary efficacy endpoint of an immune modulator could be demonstrated after at least 12 weeks*** | medication. |
| 4.3.4.4. Selection of | 06 | Comments:<br>Cytos proposes to provide an option to use a | Accepted. The guideline allows using composite scores provided validated and generally accepted. |

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| the primary endpoints Lines 420-431 | | composite endpoint. The ACQ is an example of such a composite endpoint including lung function, symptoms, activity and rescue medication use. The ACQ provides a validated composite score developed for measuring the adequacy of asthma control in clinical research studies and clinical practice with strong and discriminative properties (Juniper, O'Byrne et al. 1999).<br><br>Composite scores such as the ACQ are recommended measures to assess asthma control in clinical studies by the American Thoracic Society and the European Respiratory Society (Reddel, Taylor et al. 2009). A statistical analysis of the ACQ as an endpoint provides useful data to determine whether there is a treatment effect (and the magnitude thereof) of a medication versus a control and a clinically meaningful effect for the ACQ has been established.<br><br>Cytos believes that the ACQ is a suitable instrument to be used as a composite primary endpoint instead of co-primary endpoints in the clinical studies for immune modulators.<br><br>Proposed change (if any):<br>Controller medication<br>A new treatment should demonstrate achievement or | |

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| | | maintenance of asthma control and reduction in exacerbations. In general for a new controller treatment equal emphasis should be placed on lung function and symptom based clinical endpoints. A significant benefit from co-primary endpoints of lung function and clinical symptoms should be demonstrated so that no multiplicity adjustment to significance levels is indicated. ***Alternatively, a composite endpoint that includes lung function and clinical symptoms could also be used by a new treatment to demonstrate achievement or maintenance of asthma control.***<br><br>For new anti-inflammatory drugs exacerbations are considered the variable of choice. However, although exacerbations are described for all grades of severity, their occurrence in mild asthma may be insufficient for their use as a variable in this population. In this case other symptomatic endpoints should be selected. Composite scores to assess asthma control can be used as co-primary endpoints. Whichever score is used should be validated. The components of a composite score should be individually analysed as secondary endpoints. | |
| 7.2. Endpoints Line 590- | 06 | Comments:<br>Cytos agrees with the inclusion of composite scores to be used as primary endpoints. However CYTOS notes | Not accepted. Validated composite scores in children already reflected in the guideline. Other could be used provided adequate validation in the studied population. |

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| 593 | | that the ACQ endpoint is missing and recommend including ACQ as shown below.<br><br>Proposed change (if any):<br>In children, asthma control means minimal or no symptoms, minimal or no use of rescue medication 590 and no activity limitations. Examples of composite scores validated for use in children are Asthma Control Test (ACT), Asthma Therapy Assessment Questionnaire (ATAQ), the Asthma Control Scoring System (ACSS) ***and ACQ.*** | |
| 7.3. Trial design Lines 610-613 | 06 | Comments:<br>CYTOS proposes that immune modulators where there are no existing comparators due to the unique mechanism of action should be taken into consideration. An appropriate design should be included based on these treatments.<br><br>Proposed change (if any):<br>In children 6 years and older, in whom asthma can be reliably diagnosed, 3-arm studies (study drug – placebo – active comparator (standard of care)) are preferable. New biological treatments should be studied in comparative trials, demonstrating efficacy ~~superiority over standard treatment or~~ as add-on to standard treatment in those patients uncontrolled on ~~low dose~~ ***standard treatment.*** | Partially accepted. The study design depends not only on the MoA of the test product but also on the severity of asthma. Add-on designs are particularly recommended for severe forms of asthma, where the test product can be compared with placebo, both on top of adequate background medication. This is a priori the most suitable setting for biological medicinal products. Text revised for clarity |

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| 7.4. Safety Lines: 627-631 | 06 | Comments:<br>Based on detailed studies of the immune system (Martin, Nauta et al. 2010), the immune system is mature at 5 years of age; therefore, Cytos recommends the following changes.<br><br>Proposed change (if any):<br>New agents that interact with the immune system deserve particular attention particularly because the immune system is under development up to the age of ***6*** ~~12~~ years. Possible consequences on immune defence or immune suppression should be evaluated. The duration of action of the drug on the immune system should be documented and the duration of the clinical assessment of safety adjusted accordingly. Depending on the product the assessment of antibody formation may be necessary. | Not accepted. Complete maturation of immune system can only be confirmed at 12 years |
| Lines 94-95 | 08 | Comments:<br>The intent of the GINA Guidance's step-wise approach to management of patients who are 5 years of age and older is accurately reflected in the statement, however, the sentence itself is incomplete: "Five steps are distinguished representing each step a treatment option for controlling asthma."<br><br>Proposed change (if any):<br>"Five steps are distinguished**,** ***each*** representing ~~each~~ | Accepted. Text revised accordingly |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | ~~step~~ a treatment option for controlling asthma ***in patients 5 years of age and older***." | |
| Lines 98-102 | 08 | Comments:<br>Long-acting beta agonists are more appropriate to include under controllers rather than relievers, in line with GINA<br><br>Proposed change (if any):<br>Controllers are taken daily and long-term and include both anti-inflammatory drugs and drugs which control symptoms (inhaled corticosteroids, leukotriene modifiers, anti-IgE treatment, oral corticosteroids, ***and long-acting beta agonists***). | Accepted. |
| Lines 102-103 | 08 | Comments:<br>The following statement is misleading "Some chronic treatments are of little immediate benefit in the acute attack, for example anti-inflammatory prophylactic treatment." Oral and intravenous corticosteroids are effective for acute attacks of asthma and are widely used for their anti-inflammatory effects.<br><br>The phrase 'anti-inflammatory prophylactic treatment" is also not clear, as chronic oral steroid dosing is beneficial in reducing exacerbations, and in reducing the chance that worsening symptoms will progress to a severe exacerbation. | Accepted. |

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| | | Proposed change (if any):<br>Delete the sentence, as it could inhibit the development of newer and better anti-inflammatory drugs. | |
| Line 151 | 08 | Comments:<br>Typo: FCV should be FVC<br><br>Proposed change (if any): | Accepted |
| Lines 172-173 | 08 | Comments:<br>What is the rationale? e.g. obesity, body weight and body mass index are related to the disease status and/or benefit from treatment?<br><br>Proposed change (if any):<br>Please consider adding the rationale for such data collection. | Not accepted. Prevalence and incidence of asthma are increased in obese subjects. Response to treatment (e.g. ICS) could also be different in obese than in non-obese patients. (GINA guideline 2014) |
| Line 174 | 08 | Comments:<br>Guideline should be clear if replicate trials for each severity of asthma are required.<br><br>Proposed change (if any):<br>Please clarify | Partially accepted. Text revised. Each severity category is considered a different entity and should be studied separately if intended to be used in clinical practice. |
| Line 175 | 08 | Comments:<br>It would be useful to clarify whether a trial can include patients from different severities to conclude treatment benefit on the combined severity population. | Partially accepted. A priori, it is not expected that patients with different degrees of asthma are studied within the same clinical trials, as the study design, background medication and comparator arms may differ substantially. On the other hand, it is acknowledged that some products will only target some |

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| | | Guideline should also explain if which condition, studying only some severity is appropriate (e.g. for biologics intended to treat moderate to severe patients that have inadequately responded to medium to high dose of ICS and LABA).<br><br>Proposed change (if any): | specific subsets of patients as may not be suitable options for some degrees of severity. Text clarified |
| Line 194 | 08 | Comments:<br>As stated in the guideline, COPD and asthma may overlap. In cases where both diseases may co-exist, then defining what is predominantly COPD or predominantly asthma may not be possible and may not be useful, depending on the mechanism. Is there a definition or reference for the definition of "predominantly COPD"?<br><br>Proposed change (if any):<br>To add the definition or reference for the definition. | Text updated. There is no a formal definition of "predominantly COPD" patients. The term Asthma COPD Overlap Syndrome has recently been proposed for a patient population with a similar number of features of both asthma and COPD. A patient with more features consistent with COPD than asthma could be consider a "predominantly COPD patient" but it is not a defined term. |
| Lines 206-208 | 08 | Comments:<br>We propose adding the following subpopulations: presence of allergic comorbid conditions, and obesity.<br><br>Proposed change (if any):<br>The following examples could be considered: e.g. age, frequency of exacerbations, smoking status, known sensitivity to NSAIDs status, eosinophilia, co-sensitisations to different allergens, ***presence of*** | Accepted. |

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| | | ***allergic comorbid conditions, and obesity***. | |
| Line 212 | 08 | Comments:<br>In description of standardisation of clinical methodology, reference is made to use of diary cards. Consider just using phrase of “patient diaries” as most sponsors use electronic diaries rather than cards.<br><br>Proposed change (if any):<br>…compliance and the use of ***patient*** diary ~~cards~~. | Accepted. |
| Lines 249-251 | 08 | Comments:<br>The definition of severe exacerbations does not include death. This should be added, since not all death cases will be hospitalized or at an emergency visit before death.<br><br>Additionally, the use of corticosteroids should be clarified. It there reference to inhaled steroids or oral steroids or both?<br>Please consider the following proposed change<br><br>Proposed change (if any):<br>“Severe exacerbations of asthma are usually defined as a requirement for systemic corticosteroids or an increase ~~from~~ ***of*** the maintenance dose of ***inhaled or oral*** corticosteroids for at least three days and/or a need for an emergency visit, ~~or~~ hospitalization ***or death*** due to asthma.” | Accepted. Text revised |

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| Line 260 and elsewhere | 08 | Comments:<br>Sentence requesting justification of the change in number of exacerbations considered to be clinically relevant.<br><br>Proposed change (if any):<br>The notion of justifying clinically relevant changes in endpoints appears for exacerbations as well as other patient endpoints. Consider linking this document to the “Reflections on Patient Reported Endpoints” or suggest level of rigor required in justification of clinically relevant changes. | Not accepted, a discussion on the relevance of the results on key clinical endpoints is expected |
| Lines 261-264 | 08 | Comments:<br>This statement requires clarification: “The length of the study should be of sufficient duration to capture these events (at least 12 months) and as recruitment should continue throughout all four seasons a twelve-month follow-up is a minimum requirement”. As written it could mean that the study needs to recruit over 12 months and last for 3 months, or that after a 12 month long study another 12 months of follow up is necessary. It is not clear if the minimum 12 month follow up refers to the recruitment period or whether this refers to an additional follow up period.<br><br>The duration of asthma treatment trials should not be pre-specified, but should be discussed with and agreed | Accepted. Text revised to give flexibility. |

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| | | by the Health Authorities on a case by case basis prior to beginning the trial. In controlled clinical studies, appropriate control groups, i.e. placebo and/or comparator, should be adequately justified on scientific and ethical grounds. Justifications of the protocol design and of the potential use of placebo should be well-described in the protocol and discussed on a case-by-case basis with the relevant regulatory authorities. For example, in some studies of poorly controlled asthma, placebo-controlled trials of shorter duration, e.g. 6 months, might be sufficient to show that a new treatment reduces the frequency of asthma exacerbations. This would avoid exposing patients with severe disease to placebo treatments for unnecessarily long periods of time.<br><br>Not all the exacerbations are influenced by seasonal changes. There are cases where a 12-month study duration is unnecessary when (allergen-seasonal pollen or virus) are not essential for the induction of exacerbations. A well-defined study population is essential or prior data supporting a shorter time frame.<br><br>In addition, it may not be relevant to capture the “season” where the symptoms appear. This can be confounded by the natural history of the disease, where “normal” fluctuations of the disease occur | |

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| | | overtime.<br><br>Proposed change (if any):<br>The length of the study should be of sufficient duration to capture these events ***and dependent on the agent under study and the severity of asthma in the patient population (e.g. subject numbers, allergen triggers). The duration of asthma studies should be agreed with the Health Authorities on a case by case basis.*** ~~(at least 12 months) and as recruitment should continue throughout all four seasons a twelve-month follow-up period is a minimum requirement. During the trial it is necessary to document in what season the wheezing episodes/exacerbations occur~~. ***If the exacerbations are known to be allergy triggered it may not be necessary to document in what season the wheezing episodes/ exacerbations occurred.*** | |
| Line 267 | 08 | Comments:<br>It may be more relevant to look at the number of days with minimum asthma symptoms instead of symptom free days. This would be more consistent with definitions of level of asthma control.<br><br>Proposed change (if any): | Partially accepted. 'Number of days with minimum asthma symptoms' could be considered a relevant endpoint if the term 'minimum' refers to 'less than twice a week' as considered in GINA guideline . Otherwise the relevance of any other threshold could be questioned. 'Symptom free days' and 'Number of night awakenings' are mentioned as an example of relevant variables to be considered but other symptomatic variables could be used. |
| Line 268- | 08 | Comments: | Text revised. |

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| 269 | | "Problems of sensitivity should be taken into account..." is vague.<br><br>Clarification is needed as to what is meant by sensitivity and how it relates to symptom scores.<br><br>Proposed change (if any): | |
| Line 270 | 08 | Comments:<br>"ß$_2$ agonist" in the context of reliever medication use typically refers to short-acting ß$_2$ agonist use.<br><br>Proposed change:<br>Change "ß$_2$ agonist" to "short-acting ß$_2$ agonist" in this section. | Accepted. |
| Line 271 | 08 | Comments:<br>It may be more relevant to look at the number of days with minimum symptoms instead of frequency and intensity. This would be more consistent with definitions of level of asthma control.<br><br>Proposed change (if any): | Not accepted. The sentence mentioned established a relationship between an increase of use of a reliever medication and the frequency or intensity of asthma symptoms. |
| Line 293 | 08 | Comments:<br>Need substantiation on how to define the endpoint "reduction of controller medication". For example, a binary status of reduction or not is sufficient, or the magnitude of reduction should be considered in constructing this endpoint. If the latter, more specific | A 'reduction of controller medication' is more a quantitative than a binary variable. The magnitude of reduction considered clinically relevant should be justified by the Applicant. |

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| | | guidance is needed.<br><br>Proposed change (if any): | |
| Lines 296-298 | 08 | Comments:<br>“Eosinophil counts and fractional concentration of exhaled nitric oxide (FENO) provides information about the underlying disease activity in eosinophilic asthma.”<br><br>Exhaled nitric oxide changes are not specific to eosinophilic asthma.<br><br>Proposed change (if any):<br>Add the following sentence to the end of the paragraph.<br>“***Exhaled nitric oxide may also provide useful information about disease activity in non-eosinophilic asthma.”*** | Partially accepted. Numerous biomarkers have been tested but so far most are only considered supportive information. The guideline only gives an example. |
| Lines 299-302 | 08 | Comments:<br>In Health Related Quality of Life section, the sentence “Some asthma related QOL questionnaires are validated” and by similarity with the previous section, it would be useful to provide some examples of validated questionnaires such as the AQLQ-S, Mini-AQLQ, PAQLQ or the SGRQ.<br><br>Proposed change (if any):<br>Please consider adding the following examples: the | Accepted |

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| | | AQLQ-S, Mini-AQLQ, PAQLQ or the SGRQ. | |
| Lines 308-312 | 08 | Comments:<br>One could envisage scenarios where PD studies may be possible. In addition, it is recommended distinguishing between allergen-specific and biologics immunotherapies.<br><br>Proposed change (if any):<br>Formal pharmacodynamic studies ~~are~~ ***may*** not ***be*** possible for allergen products. However, ***pharmacodynamic studies are possible for biologic therapies, in which target interaction can be quantified (mechanism of action) and related to biomarkers and downstream disease markers. PD studies and dose- and exposure-response studies may be suitable to support dose selection.*** | Text slightly modified although initial text was intended to also cover biologic therapies. Specific reference to the relevant guideline is given for specific immunotherapy |
| Lines 314-319 | 08 | Comments:<br>ADME characteristics are important, but no mention is made of biologic immunotherapy (e.g. monoclonal antibodies) with specific, directed interaction with a target. Drugs in this class display ADME characteristics that depend on target kinetics and abundance, so Sponsors may consider exploring and reporting these target characteristics.<br><br>Proposed change (if any): | Not accepted as no specifically required, but left open for the MAH consideration. |

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| | | The pharmacokinetics of the product should be described and absorption, bioavailability, metabolism and elimination characterised. An assessment of the extent of systemic absorption of inhaled drugs and their fate is expected. Pharmacokinetic studies are not possible for products for ***allergen-***specific immunotherapy. During ***allergen-***specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the nature of the product. ***However, pharmacokinetic and PK/PD studies are possible for biologic immunotherapies (e.g. monoclonal antibodies) with specific, directed interaction with a target. Drugs in this class display ADME characteristics that depend on target kinetics and abundance, so Sponsors may consider exploring and reporting these target characteristics as well as assessing pharmacokinetics.*** | |
| Line 320 | 08 | Comments:<br>Revision of the heading is proposed, which probably is intended to read “therapeutic exploratory **studies**”.<br><br>Proposed change (if any):<br>“4.3.3. Therapeutic exploratory ~~guidelines~~ ***studies***” | Accepted. |
| Lines 321-327 | 08 | Comments:<br>This paragraph appears to contradict itself. It starts off stating that studies should be placebo controlled and | Accepted. |

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| | | suggests it may be useful to include one or more doses of an active control drug. It then goes on to suggest as an alternative inclusion of a placebo and an active control would be needed to enhance assay sensitivity. It is unclear how this constitutes an alternative. A rewording is thus proposed to clarify the paragraph.<br><br>Proposed change (if any):<br>The dose related benefit and adverse effects should be characterised in randomised, double blind, placebo controlled studies as suggested in ICH E-4 Dose Response Information to Support Drug Registration. These studies should characterise the crucial part of the dose response curve. ~~It may be useful to include one or more doses of an active control drug. Alternatively,~~ ***T***o enhance the assay sensitivity the inclusion of ~~a placebo and an active control~~ ***one or more doses of an active control*** would be needed. Study designs depend upon the pharmacology of the test drug and the response to treatment may follow a very different time course not only dependent on the drug but also on the outcome measure. | |
| Lines 328-329 | 08 | Comments:<br>It is proposed to state bronchodilator medication instead of ß2 adrenergic agonists.<br><br>It is stated that $FEV_1$ (or PEF) should be used as | Accepted. |

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| | | pharmacodynamic endpoint in dose response studies for beta2 adrenergic agonists. Clarification is requested regarding requirements for anti-inflammatory drugs, i.e. whether $FEV_1$ alone (studied for a 12-week treatment period) may also be considered as an appropriate endpoint for dose response studies for anti-inflammatory drugs.<br><br>Proposed change (if any):<br>"For ~~ß2-adrenergic agonists~~ ***bronchodilators***, a cumulative dose response may be performed..." | |
| Lines 329-331 | 08 | Comments:<br>The draft revised guideline states that in Dose-Range Finding studies for anti-inflammatory drugs, two doses of a comparator drug should be tested. A comparison to two doses of an active comparator does not seem reasonable and this is the only place where 2 doses are mentioned.<br>The need to test two doses of a comparator drug should not be a general requirement, but should be dependent on the individual substance to be tested and on the comparator itself in line with the approved dose(s) for the studied population.<br><br>For a new anti-inflammatory compound intended to be used in addition to existing treatment options, comparison to placebo on top of Standard of Care (as | Accepted. Text revised |

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| | | appropriate for the intended study population) should be allowed.<br><br>Proposed change (if any):<br>“For anti-inflammatory drugs parallel group comparative studies are likely to be necessary comparing at least two, if not, more doses of the test drug with ~~two~~ ***at least one*** doses~~s~~ of the comparator drug. ***For a new anti-inflammatory compound intended to be used in addition to existing treatment options, comparison to placebo on top of Standard of Care (as appropriate for the intended study population) is recommended.***” | |
| Lines 331-332 | 08 | Comments:<br>Clarification is requested regarding “bronchoprotection/bronchial reactivity model”, i.e. whether airway hyperresponsiveness and challenge testing (line 233) is meant. In that case consistent terminology should be used throughout the document.<br><br>Proposed change (if any): | Accepted. Text revised. |
| Lines 340 - 341 | 08 | Comments:<br>The type of bronchoprovocation test (or tests) should be specified.<br><br>Proposed change (if any):<br>For specific immunotherapy a bronchial provocation | Partly accepted. The use of methacholine challenge is up to now very limited for allergen immunotherapy and knowledge about the usefulness is lacking. May be implemented in later on if knowledge increases. |

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| | | test ***using either an allergen challenge or chemical stimulus (e.g. methacholine)***, or reduction of controller medication may be considered for efficacy analysis. | |
| Line 354 | 08 | Comments:<br>"It should be justified that efficacy is maintained without tolerance..."<br>Clarification is need as to what is meant by tolerance in this context.<br><br>Proposed change (if any): | Text revised to clarify message. |
| Line 359 | 08 | Comments:<br>Not all the exacerbations are influenced by seasonal changes. There are cases where a 12-month study duration is unnecessary when (allergen-seasonal pollen or virus) are not essential for the induction of exacerbations. A well-defined study population is essential or prior data supporting a shorter time frame.<br><br>Proposed change (if any):<br>Claims for chronic treatment with controller medication should be supported by the results from randomised, double blind, parallel group, controlled clinical trials of at least six months duration, although a longer duration may be necessary depending on the endpoint selected ~~(for example, exacerbations~~). The established use of inhaled corticosteroids as first choice controller | Accepted |

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| | | treatment for most patients makes these drugs the comparator of choice. | |
| Lines 361 - 363 | 08 | Comments:<br>The guideline should not require the parallel group design to be used in all studies of immunotherapy.<br><br>Proposed change (if any):<br>Line 363, insert “Alternative study designs should be explained and justified by the sponsor” | Accepted |
| Line 364 | 08 | Comments:<br>An addition is proposed to clarify further the statement.<br><br>Proposed change (if any):<br>The evaluation period ~~sh~~ ***c***ould cover the period of high allergen exposure (e.g. pollen season for seasonal allergens or seasonal variations for perennial allergens) ***dependent on the drug mechanism of action***. The study duration has a strong influence regarding the approvable indication (see also CHMP/EWP/18504/2006). | Not accepted. Regardless the mode of action, asthma severity in allergic asthma is dependent on allergen exposure thus the evaluation of efficacy should cover the period of high allergen exposure. |
| Line 371 | 08 | Comments:<br>Proposed to make it clear that the active control is an authorised comparator.<br><br>Proposed change (if any):<br>“... and with an ***authorised*** short acting β2 agonist...” | Partially accepted: text modified to make it clear that the active comparator should be a widely used short-acting beta 2 agonist. |

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| Lines 412-414 | 08 | Comments:<br>The NfG asks for minimal important differences to be defined and justified in protocols. These differences are often specific to the specific target population (i.e. mild vs. severe asthma) and mechanism of action.<br><br>Consider including the Reflections on PRO endpoints in the list of documents referred to in Section 3 (Line 114).<br><br>It should make it clear that the minimal clinically important difference (MCID) that is of primary interest is between active drug vs. placebo.<br><br>Proposed change (if any):<br>“For any primary endpoint selected, the minimally important difference ***compared with placebo*** should be defined …”. | Not accepted. The MCID needs to be discussed on each relevant/primary comparison, either vs placebo or vs an active comparator, anticipating that this will not be the same in the different situations. |
| Lines 421 | 08 | Comments:<br>Clarify that two of the following; exacerbations, asthma control and lung function, are recommended as co-primary (or key secondary) endpoints, depending on the population (e.g. in mild asthma, one would not chose an exacerbation endpoint). If co-primary endpoints are used, they should be chosen based on the proposed mechanism of action, the expected clinical effect and the patient population that | Accepted. |

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| | | is studied.<br>There are examples where dissociation between endpoints is observed, e.g. exacerbation and ACQ in the DREAM study (mepolizumab). The Guidance should more clearly reflect that highly targeted therapies might not improve all the major endpoints. It is possible that valuable new drugs will reduce exacerbations without necessarily having a significant effect on pulmonary function.<br><br>Proposed change (if any):<br>"….maintenance of asthma control and***/or*** reduction in exacerbations." | |
| Lines 422-423 | 08 | Comments:<br>Regarding the statement "for a new controller therapy emphasis should be placed on lung function and symptom based clinical endpoints". It is important to separate the "new controller" therapies from current biologics.<br><br>Proposed change (if any):<br>In general for a new controller treatment ***such as new corticosteroids and new long acting bronchodilator drugs***, equal emphasis should be placed on lung function and symptom based clinical endpoints. ***For highly targeted biologic therapies, improvement in a symptom based clinical*** | Partially accepted. Text fully revised. In general this should be the requirement, unless justified based on the MoA. |

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| | | ***endpoint may be of most importance.*** | |
| Lines 423-425 | 08 | Comments:<br>"... A significant benefit for co-primary endpoints of lung function and clinical symptoms..."<br>This statement seems in line if considering inhaled corticosteroids (ICS), but biologics may be more specific and less likely to impact secondary endpoints. Indeed in some cases it also might be appropriate to use a single primary endpoint and key secondary endpoints with an appropriate hierarchical statistical testing scheme. This should be mentioned in the NfG as an alternative approach to selecting co-primary endpoints. For example, a new therapy with a novel mechanism of action might be successful in improving symptoms and reducing exacerbations, while having only a minor effect on FEV1. A trial of such a therapy using co-primary endpoints ($FEV_1$ and symptom-based endpoint) would be unsuccessful.<br><br>Proposed change (if any):<br>"A significant benefit from co-primary endpoints of lung function and clinical symptoms should be demonstrated so that no multiplicity adjustment to significance levels is indicated. ***Since composite endpoints such as ACQ contain measures of lung function and clinical symptoms they should be considered as alternatives to co-primary*** | Accepted. Text fully revised. |

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| | | ***endpoints. With appropriate justification, a single primary endpoint and key secondary endpoints with appropriate hierarchical testing could be considered and discussed with the Agency."***<br><br>and after line 414, consider adding: "***The proposed mechanism of action of a new drug should be an important consideration in planning the clinical trial design and the relevant endpoints to be used***". | |
| Lines 426-7 | 08 | Comments:<br>Exacerbations are a common manifestation in severe asthma but less common in mild and moderate asthma. Therefore exacerbation may not be the variable of choice in a moderate asthma population especially if the intent is to show non-inferiority to a marketed inhaled corticosteroid. It may be more appropriate to make a composite endpoint of asthma control the variable of choice.<br><br>Proposed change (if any):<br>For new anti-inflammatory drugs exacerbations are considered ***an important endpoint to evaluate*** ~~the variable of choice.~~ | Not accepted. Exacerbations should be the endpoint of choice although the guideline allows for exceptions if justified based on asthma severity. |
| Lines 430-431 | 08 | 'The components of a composite score should be individually analysed as secondary endpoints.' | Not accepted. In general this should be done, whenever possible. |

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| | | Comments:<br>There is a repeated assertion that the component of a composite variable such as ACQ should be individually analysed. Where a time to event composite endpoint might be driven by effects on one particular event that is part of the composite analyses of the individual may be appropriate. For validated scales such as ACQ etc. there is little value in analysing each component separately (and generally this is not advised for PROs). Because each component is scored on a limited ordinal scale there is little opportunity for one component to drive the results.<br><br>Proposed change (if any): | |
| Lines 432-434 | 08 | Comments:<br>This is a high bar. Please explain rationale for “an effect on both lung function and exacerbations should be demonstrated”.<br><br>Proposed change (if any): | Partially accepted. Text revised to clarify that lung function alone is not enough. This has been previously demonstrated by LABA + CS. Deviations from this might be acceptable if justified. |
| Lines 460-461 | 08 | Comments:<br>Please specify the type of monitoring that is expected to monitor the potential for the agent to impair the leukocytes function.<br><br>Proposed change (if any): | Not accepted. To be established on a case-by case basis. |
| Line 482 | 08 | Comments: Asthma prevalence rates decrease with | Not accepted. An effort should be made to include a well |

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| | | the advancement of age, concurrent with an increase in the prevalence of COPD across age groups (Oraka, 2012). It may therefore be difficult to adequately enrol elderly patients when inclusion and exclusion criteria are designed to ensure patients with a diagnosis of COPD are not recruited.<br><br>Proposed change (if any): | characterised and homogeneous asthmatic population to properly interpret the effectiveness of the medicinal product under evaluation. |
| Line 503 | 08 | Comments:<br>The NfG should clarify what is meant by "…sufficient data should be provided to allow the adequate assessment of risk/benefit…" Does this mean that adequately powered studies should test efficacy in all three proposed age cohorts? Extrapolation of data from adolescents to younger children should be allowed in cases where the PK and PD are similar in different age groups in whom the mechanism of action of a new drug is expected to be the same. In fact, repetitive data generation across different age cohorts may be in direct conflict with the guidance provided in ICH E 11.<br><br>In the E 11 document in Section 2.4, the following text can be found: *"When a medicinal product is to be used in the pediatric population for the same indication(s) as those studied and approved in adults, the disease process is similar in adults and pediatric patients, and* | Text revised to clarify that extrapolation may be possible from adults to children over 6 years, but this should be determined on a case by case basis as severe asthma pathology might differ in children and adults, e.g. atopy vs non-atopy, absence vs presence of structural changes. In addition, there is often only insufficient information on the differences or similarities of the targeted systems (in particular for biological products) |

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| | | *the outcome of therapy is likely to be comparable, extrapolation from adult efficacy data may be appropriate. In such cases, pharmacokinetic studies in all the age ranges of pediatric patients likely to receive the medicinal product, together with safety studies, may provide adequate information for use by allowing selection of pediatric doses that will produce blood levels similar to those observed in adults. If this approach is taken, adult pharmacokinetic data should be available to plan the pediatric studies.*<br><br>*When a medicinal product is to be used in younger pediatric patients for the same indication(s) as those studied in older pediatric patients, the disease process is similar, and the outcome of therapy is likely to be comparable, extrapolation of efficacy from older to younger pediatric patients may be possible. In such cases, pharmacokinetic studies in the relevant age groups of pediatric patients likely to receive the medicinal product, together with safety studies, may be sufficient to provide adequate information for pediatric use.*<br><br>*An approach based on pharmacokinetics is likely to be insufficient for medicinal products where blood levels are known or expected not to correspond with efficacy or where there is concern that the concentration-* | |

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| | | *response relationship may differ between the adult and pediatric populations. In such cases, studies of the clinical or the pharmacological effect of the medicinal product would usually be expected.*<br><br>*Where the comparability of the disease course or outcome of therapy in pediatric patients is expected to be similar to adults, but the appropriate blood levels are not clear, it may be possible to use measurements of a pharmacodynamic effect related to clinical effectiveness to confirm the expectations of effectiveness and to define the dose and concentration needed to attain that pharmacodynamic effect. Such studies could provide increased confidence that achieving a given exposure to the medicinal product in pediatric patients would result in the desired therapeutic outcomes. Thus, a PK/PD approach combined with safety and other relevant studies could avoid the need for clinical efficacy studies."*<br><br>Proposed change (if any):<br>The NfG should contain a more explicit discussion of the situations in which data extrapolation may be applicable from adult data-sets to paediatric groups to augment the generation of PK, PD, safety data, for consideration as 'sufficient to allow for an adequate assessment of benefit / risk'. | |

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| Lines 503-505 | 08 | Comments:<br>"Sufficient data should be provided to allow the adequate assessment of risk/benefit for the three age ranges: less than six years of age, 6-12 years of age, and over 12 years of age. **A well-defined population of children need to be studied in each age subset.**"<br>Statement in Lines 504-505 does not acknowledge situation where studying a certain age group may not be feasible or scientifically justified.<br><br>Proposed change (if any):<br>Add: "A well-defined population of children need to be studied in each age subset ***unless justification for a waiver can be developed***." | Accepted. Text revised |
| Line 506 | 08 | Comments:<br>Paediatric age ranges should be consistent throughout the document.<br><br>Proposed change (if any):<br>"Specific immunotherapy in children younger than ~~5~~ ***6*** years is not recommended in general." | Accepted |
| Line 509 | 08 | Comments:<br>Addition of age range is proposed for clarity.<br><br>Proposed change (if any):<br>"The efficacy of products for specific immunotherapy | Accepted. Text revised |

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| | | has to be evaluated in special trials in the paediatric population ***(6 to 11 years of age)*** and not in combined trials with paediatric population and adults." | |
| Lines 510-511 | 08 | Comments:<br>Please clarify the statement "Adolescents and adults can be investigated as a combined population" as it relates to whether any prior assessments may be necessary to confirm these populations can be combined e.g. confirmation that the PK between adults and adolescents is consistent.<br><br>Proposed change (if any): | Not needed such clarification. PK studies will always be required |
| Lines 515-523 & 557-567 | 08 | Comments:<br>Due to improved management of asthma across Europe, demonstrating a 10% improvement in $FEV_1$ following SABA in children with asthma remains challenging and likely to result in recruitment of poorly managed or poorly adherent children. Suggest a diagnosis of asthma based on history and physical findings is sufficient and in line with clinical practise.<br><br>Proposed change (if any): | Not accepted. Text revised to clarify how to make a proper diagnosis, but recognising the difficulties in previous lung function test requirements. |
| Lines 524 - 554 | 08 | Children younger than 6 years of age<br><br>Comments: The document entitled "Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years of Age and Younger", which was | Not accepted, as the guideline already recognises the difficulties in this age group |

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| | | developed following the meeting of an expert panel in 2008 convened by GINA, addresses the particular challenges of diagnosing and managing children under 5 with asthma. In addition, it highlights the complexities of gathering data on efficacy and safety, and drug delivery of new therapeutics.<br><br>Proposed change (if any):<br>This reference should be cited in this new CHMP NfG, in order to more clearly explain the challenges related to diagnosis of asthma in this population (more than the simple statement contained in Lines 491-492 in the Section 7 introduction). These complexities can significantly undermine the successful execution of the best-designed studies within this age range. | |
| Line 553 | 08 | Comments:<br>There is a list of risk factors for recurrent wheeze in young children. It is indicated that this list should also be taken into account for older children as well.<br><br>Proposed change (if any):<br>Consider directing the reader to this issue in the discussion of asthma in children 6 years and older. | Accepted |
| Line 564 | 08 | Children 6 years of age and older<br><br>Comments: We question the appropriateness of the requirement for “induced bronchoconstriction” as a | Text revised in accordance to GINA recommendations. |

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| | | diagnostic for asthma in children aged 6 years and above – obviously particular concern would be for the younger children within that age group. We do not believe that induced bronchoconstriction should be recommended as a test to identify children for inclusion in clinical studies of asthma, because this would expose some children to unnecessary risk.<br><br>Proposed change (if any):<br>"a more suitable inclusion criterion would be ~~a > 10% drop of FEV following induced bronchoconstriction and/or~~ a 10% rise [in $FEV_1$] after inhaled short acting $\beta_2$ agonist, particularly in children aged 6-12 years." | |
| Lines 588-589 | 08 | "... The primary endpoint should be asthma control and change in lung function, using composite scores as outlined in section 4.2..."<br><br>Comments:<br>We recommend specifying that PEF is particularly relevant for children (although more so in younger than 6 years of age), in whom the technique of $FEV_1$ is not always possible to conduct or reliable.<br><br>Exacerbation as an endpoint is also valid for children as is for adults, and is thus proposed to be added as a valid endpoint. | Already covered in the text |

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| | | Proposed change (if any): | |
| Lines 590 – 593 | 08 | In children 6 years of age and older<br><br>Comments: We recommend specifying the “Childhood Asthma Control Test (C-ACT)” to set it apart from the ACT intended for use in adolescent and adult patients with asthma. Also, the ACQ-IA, an interviewer-administered version of the ACQ, is now available in several languages. Evidence for its reliability, validity and interpretability with children aged 6-10 has been reported (Juniper et al. (2010), ERJ 36: 1410-6). We therefore recommend inclusion of the ACQ-IA into the list of instruments.<br>The PACD (Paediatric Asthma Control Diary) could also be considered here.<br><br>Proposed change (if any): | Text revised to mention some of the validated text available. Any other can be used if validated and generally accepted |
| Line 597-599 | 08 | Children younger than 6 years<br><br>Comments: Clarity about the definition of exacerbations in the paediatric age group would be valuable. The way the current guidelines are written implies that a wide range of definitions is possible.<br><br>To align with comment raised below on Lines 617-619, while studies of one year`s duration are of value, shorter term efficacy studies may be considered given | As already stated in the guideline, generally accepted definitions should be used.<br>One year duration is recommended. Shorter studies can be valid for efficacy if justified based on the endpoint selected. Safety data for at least 1 year should be provided in all cases where long-term treatment is sought. |

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| | | the recognised instability of the disease phenotype in preschool children. A rewording is thus proposed with a cross-reference to section 7.3)<br><br>Current data in the literature show the lack of efficacy relative to placebo of systemic steroid bursts in treating deteriorations in children with pre-school wheeze. As a stand-alone endpoint, this is not an appropriate measure of exacerbations or loss of asthma control in children under 6 years old.<br><br>Proposed change (if any):<br>"…wheeze exacerbations (~~sufficient~~ asthma trial duration ***would need justification, see section corresponding paragraph in section 7.3***) ~~of at least one year is needed~~), ~~need for systemic corticosteroids.~~<br><br>Original articles:<br>Beigelman A, et al. J Allergy Clin Immunol 2013, 131:1518-1525.<br>Panickar J, et al. N Engl J Med 2009, 360: 329-338.<br>Oommen A, et al. Lancet 2003, 362: 1433-1438.<br>Tal A, et al. Pediatrics 1990, 86: 350-356.<br>Editorials:<br>Bush A. N Engl J Med 2009, 360: 409-410.<br>Grigg J. Atch Dis Child 2010, 95: 491-492. | |

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| Lines 599-602 | 08 | Children younger than 6 years<br>Comments: The ACQ test (actually should be referred to as the cACQ as it differs from the adult version of the test) is not recommended for use in children below the age of 6 by its developer, and we are unaware of studies supporting use in this age group. Regarding the TRACK, its recall periods are long and vary (between 4 weeks and 1 year). We therefore feel that the TRACK may be more useful in a daily clinical practice setting than as an outcomes instrument in a clinical trial. In a recently published review of the literature, the Paediatric Asthma Control Diary (PACD) showed the most consistently supportive evidence for reliability, validity and responsiveness in an asthmatic patient population below the age of 6 (Barrett et al. (2013) 42: 513-26).<br><br>Since the Children's Asthma Control Test (C-ACT) is also validated in children as young as 4, consider adding it to the list of suggested Patient-Rated Outcomes instruments.<br><br>Proposed change (if any): | Text revised |
| Lines 610-611 & 616-618 | 08 | "... In children 6 years and older, in whom asthma can be reliably diagnosed, 3-arm studies (study drug – placebo – active comparator (standard of care)) are preferable... | Text fully revised. Study design mostly based on asthma severity |

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| | | ... Currently there is little evidence of the efficacy of marketed drugs for the treatment of asthma in this age group; therefore placebo-controlled studies of one year duration are needed..."<br><br>Comments: It is difficult to reconcile the recruitment of children with uncontrolled asthma (as defined by presence of reversibility and symptoms in 6-12y, recurrent, recent symptoms and unscheduled healthcare utilisation in children <6y) with the possibility of randomisation to a placebo arm. This poses issues with regulatory authorities, ethics committees and parents.<br>It is already difficult to recruit children into placebo controlled studies but recruiting for a study with one year duration will be particularly difficult.<br><br>If placebo is essential then suggest inclusion criteria select a controlled population.<br><br>If the desire is to study uncontrolled asthma then suggest active treatment arms only.<br><br>Proposed change (if any):<br>"In children 6 years and older, in whom asthma can be reliably diagnosed, 3-arm studies (study drug-placebo- | |

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| | | active comparator (standard of care) are preferable ***in asymptomatic patients. When symptomatic children are being enrolled into studies, a placebo control arm would not necessarily be required when approved comparator medications are available and the study drug is not being added to standard-of-care treatments*.”** | |
| Lines 610-611 | 08 | Comments:<br>Clarify if the purpose of active comparator in non-biologic therapies is to benchmark the standard therapy or the intent is to establish non-inferiority / superiority of new therapy over the standard therapy.<br><br>Proposed change (if any): | Text revised. 3-arm studies preferable, particularly if the purpose is establishing non-inferiority of the new therapy over the standard treatment |
| Lines 611 – 613 | 08 | Comments:<br>“New biological treatments should be studied in comparative trials, demonstrating superiority over standard treatment or as add-on to standard treatment in those patients uncontrolled on low-dose ICS.”<br><br>Patients may be uncontrolled on low or higher doses of ICS.<br><br>Proposed change (if any):<br>Recommend removing “low-dose” from this statement. | Accepted. Text revised |
| Lines 616- | 08 | Comments: | Accepted |

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| 617 | | While there is currently “little evidence” of drug efficacy in children less than 6-years old that is not to say there is no evidence of efficacy - merely relatively few studies. This statement provides a number of problems:<br>a. The concept that children should be denied approved therapies, particularly where they are uncontrolled at randomization, represents a considerable ethical and recruitment dilemma<br>b. Where particular patient subgroups have previously been shown to be responsive to specific therapies in randomized, placebo-controlled, double-blind studies, those therapies should be allowed as appropriate comparators for that patient group, rather than placebo.<br><br>Proposed change (if any):<br>“Currently there is little evidence of the efficacy of marketed drugs for the treatment of asthma in this age group; therefore placebo-controlled studies ~~of one year duration~~ ***on top of approved standard of care*** are needed. A pre-requisite must be clear pre-specified criteria for initiation of standardized rescue treatment and for drop-out/withdrawal from the study.” | |
| Line 617-619 | 08 | Comments:<br>The requirement of studies of one year treatment duration should be revised since studies of shorter | Partially accepted. The study duration to assess efficacy will depend on the efficacy endpoint selected. Text revised to make this clear and allow some flexibility. |

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| | | treatment duration may be adequate.<br><br>Given the instability of the “asthma phenotype” within the preschool wheezing population, why is there a requirement for 1-year studies to assess efficacy? Shorter term outcomes [12 weeks was a satisfactory time-point for exacerbation assessments in these children in previous studies (Knorr et al 2001)] would be preferable as it would be difficult to separate drug efficacy issues from changes in disease phenotype over this period of time. Instability of disease phenotype is highest in children 1-3 years old. It would appear to be more sensible to restrict longer term studies to older age group based on this variability.<br><br>Please ensure consistency with other sections of the guideline, in particular with Line 506 stating that specific immunotherapy in children younger than 5 years is not recommended.<br><br>Moreover, even if we succeed recruiting children, how to deal with drop out analysis since the number of dropouts can be expected high with such a design? Please clarify.<br><br>Proposed change (if any): | Text fully revised |

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| | | "Currently there is little evidence of the efficacy of marketed drugs for the treatment of asthma in this age group; therefore placebo-controlled studies ***on top of approved standard of care*** ~~***of one year duration***~~ are needed. ***While studies of one year`s duration are of value, shorter term efficacy studies may be preferable given the recognised instability of the disease phenotype in preschool children*****.** A pre-requisite must be clear pre-specified criteria for initiation of standardized rescue treatment and for drop-out/withdrawal from the study." | |
| Lines 621-626 | 08 | Comments:<br>The number, frequency and invasiveness of assessments in children participating in clinical trials need to be minimised to those which are absolutely necessary. If the risks of systemic effects are known through well-characterised PK and PK/PD models, then specific assessments can be omitted in favour of routine AE monitoring.<br><br>Proposed change (if any): | Accepted. No changes required |
| Line 633 | 08 | Comments:<br>"RMP" is ambiguous; please write out "RMP" as Risk Management Plan. Also consider including description of the RMP in Section 3 (Line 114)<br><br>Proposed change (if any): | Accepted |

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| Lines 634 - 664 | 08 | Comments:<br>The section on delivery devices is important not only for children but also for the elderly. Should it be a separate section apart from 7 Studies in Children? Nebulizers are not only used by children but also by the elderly. Consider making the section on delivery devices a separate section covering the use of delivery devices in children and the elderly.<br><br>Moreover section 7.5 addresses only inhalation delivery devices. No guidance is supplied for biologic therapies, which may be given IV or SC via various devices. Consider changing title to "***Selection of inhalation delivery devices***." | Not accepted but point taken. Reference is also included in the corresponding section on elderly |
| Line 638 | 08 | Comments:<br>It is unclear why the spacer would need to be a named device.<br><br>Proposed change (if any): | |
| Line 642 | 09 | "For children aged 6 (replace:4) years and older a dry powder inhaler (DPI) may also be considered"<br><br>**Recommendation:** replace "6" with "4" years and older to allow consideration of the 4-6 year old patient population as candidates for some suitable DPIs. | Accepted. Text revised |

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| Line 644 | 09 | "Therefore [add: in vitro] characterisation of flow rate dependency in the patient populations in whom the DPI is to be used should be presented"<br>**Recommendation:** add "in vitro" to distinguish vs/exclude requirements for lung deposition studies in small children. | Not accepted. Reference is made to the OIP guideline |
| Line 662 | 09 | Inhaler devices intended for the paediatric population should include a dose counter and [add:/or] feedback should be provided to patients/caregivers on the correct use of the inhaler"<br>**Recommendation:** replace "and" with "and/or", feedback mechanisms (e.g. a red/green indicator window) can also ensure patient compliance after every dosing | Text revised. |
| 151-153 | 10 | Comments:<br>Dose, type, time are missing. We propose to add an example as in the GINA document<br><br>Proposed change (if any):<br>The reversibility of FEV1 after inhalation of a short-acting β2 adrenergic agonist (a few minutes after inhalation of an eq of salbutamol 200-400 mcg) should normally be greater than 12-15% and 200 ml. | Not accepted. Clinical guidelines should be followed, but this is not expected to be such that. |
| 163 - 164 | 10 | Comments:<br>Will be difficult to assess! Should be tuned<br><br>Proposed change (if any): | Accepted |

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| | | Patients randomised to study treatments should be **free from symptomatic/ acute respiratory infection** | |
| 165 | 10 | Comments:<br>Use "allergen immunotherapy" all over the document (Calderon et al. Allergy 2013; 68: 825-8)<br><br>Proposed change (if any):<br>For clinical studies to investigate the efficacy of **allergen immunotherapy** the patients…. | Accepted. |
| 169 - 171 | 10 | Comments:<br><br>Proposed change (if any):<br>The inflammatory profile should be characterised if this is relevant to the mechanism of action of the test drug; for example, baseline eosinophilia, **fractional concentration of exhaled nitric oxide (FENO)**, IgE production or cytokines if that aspect of the immune system is targeted by the investigational product. | Accepted |

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| 207 - 208 | 10 | Comments:<br>- WAO-EAACI nomenclature suggest to use "hypersensitivity"<br><br>- More than sensitization, allergy is important<br><br>Proposed change (if any):<br>The following examples could be considered: e.g. age, frequency of exacerbations, smoking status**, known hypersensitivity** to NSAIDs status, eosinophilia, and **sensitisations and sometimes clinical relevance of sensitisations to allergens** to different allergens. The selection of the most relevant subpopulations should be made on a case by case basis. Consistent effects in relevant sub-populations should be shown. | Accepted. |
| 223 | 10 | Comments:<br>Should say how reproducibility and sensitivity should be showed and when (are published proofs enough?)<br><br>Proposed change(if any): | Text revised. |
| 249 - 251 | 10 | Comments:<br>An increase from the maintenance dose of inhaled corticosteroids for at least three days should not be considered as a severe exacerbation of asthma but only as a moderate exacerbation<br><br>Proposed change (if any): | Accepted. Definition revised in line with clinical guidelines |

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| | | Severe exacerbations of asthma are usually defined as a requirement for systemic corticosteroids or a need…. | |
| 308 - 311 | 10 | Comments:<br>Both the changes in allergen specific IgG levels and in bronchial reactivity (e.g. allergen dose threshold,…) are weakly related to the dose of allergen administered as a specific immunotherapy and are not relevant to predict clinical efficacy.<br><br>Proposed change (if any):<br>However, to show the effects of specific immunotherapy on the immune system, immunological changes (e.g. changes in allergen specific IgG levels,…) and/or modifications of end organ specific response (e.g. provocation tests) **could be** measured. | Not accepted. It is right that changes in allergen-specific IgG levels or bronchial reactivity cannot predict the level of clinical efficacy. However, this is not the issue for this kind of studies. This kind of studies should show a modification of the immune-system and thus the pharmacodynamics of the allergen product. And this is indeed possible. Since there are no other pharmacodynamics studies possible for this kind of therapy, such parameters **should** be measured. |
| 386 - 387 | 10 | Comments:<br>Proposed change (if any):<br>A third arm with a standard upgrading comparator should be considered. **The comparator(s) should correspond to the next medication step according to guidelines (i.e. increase in inhaled corticosteroid dose or adding a long acting bronchodilator to inhaled corticoids). However, in patients already receiving optimal dose of inhaled corticosteroid associated with a long acting bronchodilator upgrading in a third arm** | Accepted as proposed. |

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| | | **with monoclonal antibody-based therapies (i.e. anti-IgE, anti-cytokines) is not mandatory.** | |
| 421 | 10 | Comments:<br>In case of study in controlled patients (maintenance of asthma control), the number of exacerbations is very weak.<br><br>Proposed change (if any):<br>A new treatment should demonstrate achievement or maintenance of asthma control **or** reduction in exacerbations. In general for a new controller treatment equal emphasis should be placed on lung function and symptom based clinical endpoints | Accepted with and/or instead of or. |
| 467 | 10 | Comments:<br>All of them?<br>What is the decision if not all are looked for: medication not approved?<br><br>Proposed change (if any): | Not accepted. This is something that should be discussed on a case by case based on study drug, and justifying any missing DDI that would be of relevance. |
| Section 4.1 | 11 | In general the Faculty welcomes this updated guidance. We have a few specific comments:<br><br>This section discusses the selection of patients based on confirmation of asthma diagnosis by 12% change (or 200mL) in $FEV_1$ with a standard dose of bronchodilator. We have two concerns about this: 1) | Not accepted. It is currently included. |

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| | | Although the EMA mention the concept of 'well controlled' patients, this is only mentioned briefly (lines 153-154) that this may be difficult to attain – that sentence should be expanded to include clear reference to historical data on reversibility, (2) children under ~age 5-7 will find it difficult to perform spirometry (varies depending on paediatric pulmonary function expertise), but more should be stated in this section about other objective (airway) assessments for children.<br><br>Proposed change (if any): | |
| Section 4.1, line 163 | 11 | 'patients…should be free from infection' – does the EMA have a view as to how long they should have been infection-free? (In trial protocols periods of 2wks to 3mths have been used). Most industry sponsored studies will exclude those with a recent history of URTI within at least last 2 weeks for stable asthma studies. | Partially Accepted, but this is left to the sponsor |
| Section 4.1, lines 195-201 | 11 | Inclusion of smokers is a difficult issue, clearly they should be studied, but ethically every effort should be made to get them to stop; if they do so during the study it may affect the results. Perhaps expanded guidance could be given here? Most industry sponsored studies of asthma will exclude smokers for one (or both) of two reasons: 1) if patients are still smoking, despite every effort of their carers to help | Not accepted. The important issue is to characterise them properly and to perform adequate analysis in this subset of patients. |

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| | | them stop, can they be expected/trusted to follow often detailed protocol instructions like recording PEF and symptoms on electronic diaries twice daily for many weeks and 2) especially for those >40 years of age, they are almost certain to have some irreversible obstruction making their airway disease “mixed”. Most industry programs will specifically be seeking “clean”, homogeneous populations. | |
| Section 4.2, lines 216-221 | 11 | Pre-bronchodilator FEV1 is the most suitable measure in most situations but for assessment of immediate bronchodilator effect (e.g. a ‘reliever’ inhaler) clearly post-bronchodilator FEV1 is required. Most industry studies would expect to have a very detailed section on how to measure $FEV_1$ which should be recorded in clinic by properly trained and accredited respiratory function technicians, nurses or doctors to ATS/ERS criteria. In addition $FEF_{25-75}$ may be a more sensitive tool for early diagnosis and clinical studies of milder asthma. PEF recordings (and $FEV_1$) can now be captured in electronic diaries that date and time stamp entries and the diurnal and period variability of PEF can be a useful guide to asthma control, or lack of it. | Not accepted. The guideline states that pre-BD is the preferred but other measures can be used if justified. |

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| Section 4.2, lines 236-7 | 11 | 'challenge testing….for specific immunotherapy'. It is not clear if this refers only to allergic desensitisation protocols, or would include any agent with presumed anti-allergic effect e.g. anti-IgE, anti-IL-4. Allergen challenge can of course be used to evaluate the protective effects of a simple bronchodilator. Many drugs that enter the clinic undergo phase 1 testing and then go into a human Late Asthmatic Response asthma challenge test in mild asthmatics conducted under carefully controlled conditions. | Not accepted. |
| Section 4.2, lines 265-6 | 11 | There are certainly validated scales for asthma control (e.g. ACQ) which includes symptoms. Symptoms have been scored for many years by several different methods which have been validated as well as collected as components of numerous wider ranging Quality of Life Questionnaire (such as the SGRQ) and specific Asthma questionnaires (ACQ and AQLQ). | ACQ is already included in the composite scores section. |
| Section 4.2, line 274 | 11 | 'bronchodilator' rather than 'beta-agonist'? asthmatics do use short-acting anti-cholinergics as relievers. | Accepted. |
| Section 4.2, lines 293-4. | 11 | Agreed, but patients are often maintained on too high a dose of ICS and can reduce it considerably even without additional medication, making this a difficult endpoint. | Not accepted. If this endpoint is selected, it should be ensured that only patients on adequate treatment are included. Otherwise, results could not be interpreted. |

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| Section 4.3.1, line 310 | 11 | Should this be 'allergen specific IgE levels', rather than 'IgG'? | Not accepted. IgG levels were meant. Change in IgE is often not measurable or only measurable as "no increase" during pollen season. In contrast, increase in allergen-specific IgG (especially IgG4) is always present if the immune-system is modified. Text revised to make reference to the specific guideline. |
| Section 4.3.2, line 317 | 11 | Again, is 'specific immunotherapy' restricted to allergen desensitisation? Clearly PK can be performed on anti-IgE therapy, for example. | Accepted. Text revised. |
| Section 4.3.3, line 331 | 11 | Why would it be necessary to compare against more than one dose level of a licensed comparator drug if it is only approved for use at one dose? | Accepted. Text revised for clarity. |
| Section 4.3.4 (study design) | 11 | General comment; there is no mention of continuing to study patients after they stop the investigational drug, to see for how long any beneficial effect is maintained (i.e. is the drug potentially disease-modifying). We would recommend a 28 day follow up after a chronic dosing, phase 2 or 3 study. | This type of assessment would be welcomed, but a longer duration might be required to substantiate the "disease-modifying" claim. No regulatory experience exists with this type of approaches. Scientific advice would be recommended. |
| Section 4.3.4.1, line 354. | 11 | This should apply also to some types of controller medication; LABAs may exhibit tolerance (receptor downregulation) after 6 weeks or more. Studies have often been of 12 weeks duration for pivotal controller medication asthma programs – that has been sufficient in the past to demonstrate efficacy versus both active and placebo comparisons. Where the active control is an inhaled steroid (ICS), methods for blinding have to | General message accepted. Characterisation of patients is critical as well as the adequate control of patients during study. |

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| | | carefully spelt out – and may involve double dummy design. The ICS may need to be withdrawn some time before subjects are randomized to treatment and this can give ethical concerns especially in more moderate patients, thus a new controller may be tested initially at least In addition to current controller medication. If the trial involves reducing dose or discontinuation of controller it is customary and expedient to set strict criteria for “asthma deterioration” necessitating withdrawal of the subject form the study, reinstating them on their previous controller medication and following them up to ensure asthma control has been regained. | |
| Section 4.3.4.3. (Lines 403-405) | 11 | “The need in all cases … for an independent adjudicating committee to assess safety and efficacy”. We disagree with this. Provided GCP has been followed, data collected and stored according to a predefined protocol, data management plan, the database locked once all data has been verified and entered the sponsor can assess the safety and efficacy of the drug. | Accepted. It is just a recommendation. |
| Section 5.1 | 11 | Long term safety. While 12 months studies are not unreasonable, for a new non-steroid controller, we would ask that the EMA introduce more flexibility and perhaps require 12 month safety (including growth) as a post marketing safety study/phase IV commitment. The exact mechanism of action of any new drug should | This is in line with ICH for chronic therapies. Not accepted. |

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| | | be considered when defining safety surveillance, as well as preliminary clinical and previous preclinical data. | |
| Section 6, line 485. | 11 | For breath-actuated and dry-powder devices perhaps a specific study of ability to generate sufficient inspiratory flow-rates should be recommended (also for children, see section 7.5, line 644) | Accepted. No changes needed. |
| Section 7 Paragraph 1. | 11 | The FPM understood that the whole purpose of the Paediatric Investigation Plan (or PIP) was to ensure industrial sponsors had to have specific plans for paediatric studies for the EMA to consider an MAA? Why is that not mentioned in this section? | Text revised |
| Section 7, line 522. | 11 | Induced bronchoconstriction by e.g. methacholine is potentially hazardous; is exercise-induced bronchoconstriction intended here? | This is not a mandatory requirement |
| Section 7, line 541. | 11 | Suggest adding 'and non-cystic fibrosis bronchiectasis' | Not considered needed |
| Section 7.2 | 11 | There are other specific paediatric asthma questionnaires that have been validated and widely used by industry. | The guideline includes some examples of validated and generally accepted composite questionnaires. This is an evolving field and cannot be expected to be updated in this regard |

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| 174 | 12 | Comments: Guideline text: 'In principle for a new product it is expected that separate studies are carried out for each grade of asthma severity for which the new product is intended to be used'...<br>Indication for SIT is made for a timeframe of 3 years according to WHO and therefore it may be appropriate to include patients of all GINA treatment steps except for step 5. The stepwise treatment approach according to GINA is very helpful for the management of asthma control but not for start and stop decision of SIT treatment. We do not expect different mode of actions in the treatment steps. SIT is a causal treatment in allergic asthma with immunologic effects in different asthma steps. In addition during long-term treatment periods of SIT it is anticipated that patients may step through several level of asthma severity and asthma control (e.g. during exposure in pollen season). For safety reasons all patients have to be controlled during SIT so that a differentiation according to severity levels will not be possible.<br><br>Proposed change (if any): Following the current text: In clinical trials for specific immunotherapy (SIT) it may be appropriate to include patients with different severity classes, e.g. GINA treatment step 2-4 if they are controlled during SIT. | Partly accepted. Reworded. |

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| 236 | 12 | Comments: In specific immunotherapy trials the number of regularly performed provocation tests (e.g. skin provocation tests, environmental challenge chambers, conjunctival provocation tests) are quite frequent. Therefore it should be clear that specific bronchial allergen provocation should be limited to a subgroup of patients.<br><br>Proposed change (if any): Challenge tests with an appropriate allergen can be considered in clinical studies for specific immunotherapy. Allergen specific bronchial provocation test should be limited to a subgroup of patients to limit risk and burden to the patients. | No change needed as bronchial provocation tests are only accepted as exploratory endpoints and/or for dose-finding. Thus, the number of patients will be limited. |

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| 340 | 12 | Comments: The guideline CHMP/EWP/18504/2006 for the clinical development of products for specific immunotherapy for the treatment of allergic diseases must been taken into consideration. Since the pathological mechanisms of allergic rhinoconjunctivitis and allergic asthma are very similar, i.e. both are considered an IgE mediated disease, the efficacy of specific immunotherapy can be investigated with routine allergy efficacy endpoints.<br><br>Proposed change (if any): For specific immunotherapy provocation tests as described in guideline CHMP/EWP/18504/2006 or reduction of controller medication may be considered for efficacy analysis. | Provocation test is allowed as bronchial provocation and reduction of controller medication is allowed. Other provocation tests (conjunctival and or nasal provocation test) are only useful in patients with allergic rhinitis, which may be but has not to be necessarily comorbidity with allergic asthma. However, environmental exposure chamber is included. |
| 559 | 12 | Comments: Classification of asthma severity as outlined in section 4.1 (lines 180-191). '…(line 189) COPD and asthma have different aetiologies but may coexist in the same patient.'<br><br>Text till line 188 would be correct as COPD and Asthma should not be evaluated in children.<br><br>Proposed change (if any):Classification of asthma severity as ountlined in section 4.1 (lines 179-188) | Text revised |

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| 596 | 12 | Comments: Line 506 'Specific immunotherapy in children younger than 5 years is not recommended in general.'<br>This general recommendation is in contrast to specific immunotherapy preparations with an approval for the age of four.<br><br>Proposed change (if any): | Text revised |
| 503 cont. | 12 | Comments:<br>Line 503: 'Sufficient data should be provided to allow the adequate assessment of risk/benefit for the three age ranges: under six years of age, 6-12 years of age, and over 12 years of age'.<br>In specific immunotherapy trials the age groups should be harmonized with CPMP/ICH/2711/99, ICH Topic E 11:'Clinical Investigation of Medicinal Products in the Paediatric Population' and the EMA paediatric regulations. The age groups from 4 to <6 should be included in the age group 2-11 as mentioned in ICH Topic E11. The authors should explicitly allow other age groups for specific immunotherapy in the indication of asthma. | Text revised |
| Lines 261-264 | 13 | Comments:<br>We experienced this has been interpreted by some that exacerbation studies should be 2 years in length (12 month randomization period, 12 month follow up). | Text revised for clarity. |

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| | | As most 12 month studies will maintain the majority of subjects in the trial for the duration of treatment and accommodate the agency's desire for evaluation of the population through the seasonal cycle.<br>This should be revised to be clear that this should be a 12 month study with a recruitment period that spans 12 months to accommodate all seasons.<br><br>Proposed change (if any):<br>The length of the study should be of sufficient duration to capture these events (at least 12 months), with a recruitment period that spans twelve-months to accommodate all seasons. During the trial it is necessary to document in what season the wheezing episodes/exacerbations occur. | |
| Line 265-266 | 13 | Comments:<br>**"Symptom scores:** Assessment of symptoms is an acceptable clinical variable although there are no 265 validated scales. Both daytime and night-time symptoms should be recorded".<br><br>The use of Likert scale assessments has been the standard means of assessing symptoms in most respiratory programs. We would like to have the opinion of EMA on whether they view this as acceptable given this has become the industry standard and the basis for derived variables such as | Accepted. Text modified. |

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| | | "symptom free days". This opinion should be reflected in the guideline.<br><br>Proposed change (if any): | |
| Line 420-427 | 13 | Comments:<br>It should be clarified whether the definition of exacerbation here can be "moderate exacerbations" and whether study duration is required to be 12 months (vs 6 months) if this indication (i.e. prevention of exacerbations) is not being sought).<br>Based on the current wording, it appears the requirements for registering potential controller medications have substantially been raised on line 421, while lines 422 and 427 seem to suggest lung function and symptom based endpoints are adequate. The guidance needs to be clear what is required and whether the intent is to require a year long pivotal study(ies) for controller medications with anti-inflammatory properties as the wording on 421 implies.<br><br>Proposed change (if any): | Partially accepted. Text revised for clarify on requirements |
| Line423-425 | 13 | Comments:<br>"A significant benefit from co-primary endpoints of lung function and clinical symptoms should be demonstrated so that no multiplicity adjustment to significance levels is indicated". | Text revised for clarity |

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| | | We would like clarification on this, as current language seems to contradict standard guidance on how multiple endpoints identified as co-primary should be handled.<br><br>Proposed change (if any): | |
| Line 432-434 | 13 | Comments:<br>Similar to comments above: we would like to have clarification if this does require a 12 month program or is 6 months adequate with use of “moderate exacerbations” as an acceptable co-primary endpoint to demonstrate effect.<br><br>Proposed change (if any): | Text revised for clarity on the required treatment duration |
| Line 617-618 | 13 | Comments:<br>“…therefore placebo-controlled studies of one year duration are needed.”<br><br>It is not clear that this would be viewed as an ethically acceptable approach in Europe. Flexibility in duration of study (12 months) would be highly advisable.<br><br>Proposed change (if any): | Text clarified |
| Line 651 | 13 | Comments:<br>“All medications delivered via pMDI should always be administered with an age appropriate spacer device attached.” | Accepted |

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| | | Given the individual product characteristics of medications delivered by pMDI, mandated use of spacer devices should be cautiously considered as these devices can have unpredictable and sometimes paradoxical effects on actual drug delivery. | |
| 96-103 | 14 | Comments:<br>For homogeneity purpose, the specific information on allergen specific immunotherapy should be put at the end of the section, as presented in the other sections<br>Proposed change:<br>The GINA Workshop Report classifies drug treatments as controllers or relievers. ~~In addition, Allergen-specific immunotherapy is available for allergic asthma although its specific role is not completely established yet~~<br>Controllers are taken daily and long-term and include both anti-inflammatory drugs and drugs which control symptoms (inhaled corticosteroids, leukotriene modifiers, anti-IgE treatment, oral corticosteroids).<br>Relievers are medications used on an as-needed basis to reverse bronchoconstriction and relieve symptoms. Examples of relievers include rapid-acting bronchodilators (e.g. short- and some long-acting β2 agonists). Some chronic treatments are of little immediate benefit in the acute attack, for example | Accepted. Text revised. |

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| | | anti-inflammatory prophylactic treatment.<br>**In addition, Allergen-specific immunotherapy is available for allergic asthma although its specific role is not completely established yet.** | |
| 174-176 | 14 | Comments:<br>The asthma status of the patients may vary along the treatment due to the nature of the disease; it is more relevant to consider the population more globally.<br>Proposed change:<br>The risk posed by asthma depends upon its severity. In principle for a new product it is expected that **a number of patients representative for each** ~~separate studies are carried out for each grade of~~ asthma severity for which the new product is intended to be used. | Not accepted. Data provided should allow a B/R discussion separate for each subset of patients. The guideline may allow this type of mixed studies as exceptions and provided that fulfils a number of requirements for assessment. |
| 261-263 | 14 | Comments:<br>Clarification is requested on the word “follow-up”<br><br>Proposed change (if any):<br>The length of the study should be of sufficient duration to capture these events, a minimum of 12 months~~ and as recruitment should continue throughout all four seasons a twelve-month follow-up is a minimum requirement~~. | Accepted. Text revised. |
| 369 - 387 | *14* | Comments<br>Could it be clarified that because the role of Allergen-specific immunotherapy is not completely established | Not accepted. The executive summary highlights that no specific recommendations for allergens are given due to the limited regulatory experience. Scientific advice is |

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| | | yet, recommendations applicable to use of comparators for reliever and controller medications may not be relevant for Allergen-specific immunotherapy | recommended. |
| 389 - 390 | 14 | Comments:<br>Clarification would be appreciated; how far this should be considered, knowing that depending on the objective of the study, partly controlled or uncontrolled patients can be selected? | The key issue is to properly characterise the study population. Interpretation of possible changes in concomitant medication and use of rescue will be done accordingly. Text modified slightly for clarity |
| 436 - 437 | 14 | Comments:<br>The efficacy of Allergen Immunotherapy has been confirmed in reducing symptom scores and medication requirements, i.e. Allergen Immunotherapy has the potential to control asthma (GINA, updated 2012).<br><br>Proposed change (if any):<br>Products for specific immunotherapy are intended to modify the immunological mechanism underlying allergic asthma **improving its control** and thus require some time for onset of action. | Not accepted. This should be demonstrated for a given product, independently of the MoA |
| 439 - 440 | 14 | Comments:<br>Allergen Immunotherapy being not a reliever treatment, lung function should not be considered as a primary endpoint.<br><br>Proposed change (if any):<br>~~Lung function,~~ Composite scores, number of | A priori, it is expected to see some effect on lung function, given the reversibility/inflammatory component of the condition. As it is mentioned that these endpoint **could** be considered, no change is necessary. |

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| | | exacerbations or reduced need for controller medication could be considered as primary endpoints. | |
| Lines 94-95 | 15 | Comments:<br>It is not clear how the 5 treatment steps relate to the severity terms of mild, moderate or severe. We suggest at least clarifying that the relation should refer to an international guideline, to avoid different ad hoc definitions from different sponsors and different products.<br><br>Proposed change (if any): | Accepted. Text revised according to last GINA guideline 2014 |
| Lines 174-175 | 15 | Comments:<br>The sentence stating with "In principle..." can be read as if separate studies are required for each treatment step - i.e. 5 trials to cover the entire spectrum of asthma. We would assume that the intention is to establish that trials have to cover the full population in which an indication is sought without dictating a separate trial for each treatment step.<br><br>The link between treatment steps and "mild/moderate/severe" is unclear. Again, we suggest at least establishing that this link must be made by referring to an international guideline, i.e. sponsors are not free to make their own ad hoc definitions.<br><br>Proposed change (if any): | Text revised for clarity |

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| | | In principle for a new product it is expected that separate studies are carried out for each grade of asthma severity for which the new product is intended to be used. For products that are not classified as controllers or relievers, a single study addressing the treatment steps included in the intended indication may be appropriate. The criteria used to classify severity of asthma should be clearly established in the protocol as the current clinical classification differs from that stated previously in treatment guidelines. | |
| Lines 175-176 | 15 | Comments:<br>Stating that "the criteria used to classify severity should be clearly established…" opens up for separate classifications in each and every protocol, which will only worsen the confusion regarding asthma severity/control levels. We would prefer a clearer guidance on what is considered mild, moderate or severe asthma from the EMA point of view, e.g. a reference to an international treatment guideline or at least a statement that an international guideline should be used when defining severity.<br><br>Proposed change (if any): | Text revised according to GINA 2014 |
| Lines 196-198 | 15 | Comments:<br>The sentence starting with "Any subgroup…" implies that a trial should be powered for showing efficacy in smokers. A logical consequence of this could be that | Subgroup analyses are not usually aimed to demonstrate statistically significant results but rather a consistent effect to that seen in the overall population. Not accepted. |

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| | | e.g. smokers are excluded from the clinical trials since powering trials to show statistical significance in all subgroups will be impossible. In our opinion, trials should be powered for analyses of the primary endpoints in order to meet the primary objective, not for subgroup-analyses.<br><br>Proposed change (if any): | |
| Lines 203-205 | 15 | Comments:<br>Stratification should always be balanced carefully - and should not be included as a requirement. We find that this formulation may be interpreted as if it is required to stratify. We suggest referring to ICH E9 for guidance on stratification.<br><br>Proposed change (if any): | Not accepted. The text clearly states that stratification “could be” considered, it´s not a requirement. |
| Lines 209-210 | 15 | Comments:<br>What is meant by consistent effects - and relevant sub-populations? We suggest specifying that it is required that "efficacy should be shown in all sub-populations included in the indication". We do not agree that the effect size should be the same for all sub-populations. It is possible to have sub-populations with e.g. a lower effect than others but still benefitting from treatment if no other treatment option is available. | Not accepted. General principles established in BSWP EU Guideline |

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| | | Proposed change (if any): | |
| Lines 215-302 | 15 | Comments:<br>Consider changing the order of the efficacy endpoints, to put the most important endpoints first. Further we suggest to put challenge testing at the bottom of the section, as this must be considered an exploratory endpoint for the time being due to the lack of agreed cut-offs and the limitations induced by the difficulties in conducting provocation tests consistently in multi-site trials.<br>Proposed order:<br>Lung function, Asthma Exacerbations, Symptom Scores, Reliever use, Reduction of controller medication, composite scores, Airway hyperresponsiveness and challenge testing, Biomarkers of airway inflammation, Health related quality of life.<br><br>Proposed change (if any): | Accepted. Text revised. |
| Lines 216-228 | 15 | Comments:<br>We recognise the inclusion of different methods for measuring lung function depending on trial setting and consider this very important.<br><br>Proposed change (if any): | Not changes required. |
| Lines 233-237 | 15 | Comments:<br>We consider challenge testing a grey zone, as no | Changes not needed. |

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| | | agreed cut-offs exists and thus the results will not be suitable for efficacy measurements. Further there are significant limitations in the use of challenge testing as an efficacy endpoint due to the difficulties in conducting these tests consistently across sites in multi-site trials.<br><br>Proposed change (if any): | |
| Lines 249-258 | 15 | Comments:<br>We find it good that exacerbations according to their severity are clearly defined, and that the importance of moderate exacerbations is stated.<br>We suggest using the definition from ERS/ATS of "moderate and severe exacerbations" (Reddel, 2009) to aid consistency in asthma trials. The current text can be interpreted as if increased use of inhaled corticosteroid for 3 days should be judged as a severe exacerbation; this is in contradiction to the most commonly used definitions in the available literature<br><br>Proposed change (if any):<br>Severe exacerbations of asthma are usually defined as a requirement for systemic corticosteroids or an increase from the maintenance dose of systemic corticosteroids for at least three days and/or a need for an emergency visit, or hospitalization due to asthma. It is recommended to use the definition of | Partially accepted. Clarification on the preferred definitions clearly stated. |

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| | | moderate and severe exacerbations from ERS/ATS unless otherwise justified. | |
| Line 260 | 15 | Comments:<br>We suggest to change the wording "change in number of exacerbations..." to "change in the primary endpoint thought to be..." as this may not be numbers of exacerbations but hazard rate - if time to event [asthma exacerbations] is defined the primary analysis<br><br>Proposed change (if any):<br>The methods used to capture (as percentage of patients, annualized rate, time to event) and analyse this endpoint should be justified as should the change in the primary endpoint thought to be clinically relevant. | Accepted. Text modified to address this concern. |
| Lines 261-263 | 15 | Comments:<br>We suggest softening the wording regarding the duration of trial in case asthma exacerbations is the primary efficacy endpoint. We do not see a rationale for the "at least 12 months"-criterion for capturing events, and also not for the recruitment during all 4 seasons. For a trial on treatment of seasonal allergic asthma this would be unnecessary. A possibility for a wording allowing for differences between various treatment modalities and their objectives and mode of action could be to change to "sufficient duration to capture the relevant events and thus to support the | Accepted. Text modified to address this issue. |

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| | | indication". By putting strict requirements on this endpoint and no requirements for duration on any of the other endpoints, the risk is that no investigations on asthma exacerbations will be performed.<br><br>Proposed change (if any):<br>The length of the study should be of sufficient duration to capture the relevant events and thus to support the indication. | |
| Line 265 | 15 | Comments:<br>Good that symptom scores are acceptable endpoints, however it would be helpful if recommendations on which tools/scales to use were included in order to support validation and standardisation.<br>Symptom scores could be assessed using the following scale: A total of 4 daytime asthma symptoms are measured daily on a scale from 0 to 3 (0=no symptoms, 1=mild symptoms, 2=moderate symptoms, 3=severe symptoms). The 4 symptoms are cough, wheeze, chest tightness/shortness of breath, and exercise-induced symptoms.<br>Night time asthma symptoms could be assessed in the same way.<br><br>Proposed change (if any):<br>Both daytime and night-time symptoms should be recorded. The following scale could be used: 4 asthma | Partially accepted. There is no optimal scale. Reference is however made in the guideline to the most commonly used scale. |

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| | | symptoms (cough, wheeze, chest tightness/shortness of breath, and exercise-induced symptoms) measured morning and evening on a scale from 0 (no symptoms) to 3 (severe symptoms). The use of diaries is encouraged, preferably electronic diaries to enhance accuracy of recording. | |
| Lines 268-269 | 15 | Comments:<br>Regarding the sentence starting with "Problems of sensitivity…": we do not understand this sentence, please elaborate<br><br>Proposed change (if any): | Text revised. Accepted. |
| Lines 273-274 | 15 | Comments:<br>It may not be simple to record and report β2-agonist use as prophylaxis and relief separately. We suggest that instead of "should be" the guidance is change to "The use of β2 agonists for the relief of symptoms versus prophylactic use should be considered in the protocol and when relevant reported separately".<br><br>Proposed change (if any):<br>The use of $\beta_2$ agonists for the relief of symptoms versus prophylactic use should be considered in the protocol and when relevant reported separately. | Only partially accepted. Text revised |
| Lines 289-290 | 15 | Comments:<br>Consider replacing "should be" with "could be" - the analysis should always be predefined, but may include | Accepted. |

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| | | better ways of analysis than the proportion of subjects. Further the cut-offs (e.g. from controlled to partly controlled) are not clearly defined for the questionnaires and not necessarily in agreement with e.g. GINA or NAEPP guidelines<br><br>Proposed change (if any):<br>The analysis of the composite variable could be provided in absolute terms and as a proportion of patients achieving a defined target level of control. | |
| Lines 291-292 | 15 | Comments:<br>In the "Points to consider on multiplicity issues in clinical trials, CPMP/EWP/908/99" the handling of composite endpoints, it is stated that "treatment should beneficially affect all components, or at least should the clinically more important components not be affected negatively. Any effect of the treatment in one of the components that is to be reflected in the indication should be clearly supported by the data." We suggest aligning the text here to reflect this, or to delete the sentence on components and instead refer to CPMP/EWP/908/99.<br><br>Proposed change (if any): | Accepted. |
| Lines 299-302 | 15 | Comments:<br>Good that QoL instruments (generic and disease specific) are mentioned and recommended as | General comment. |

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| | | acceptable endpoints.<br><br>Proposed change (if any): | |
| Lines 423-425 | 15 | Comments:<br>The sentence is unclear. We suggest to stop the sentence after "…should be demonstrated." If found required, we suggest to refer to the "Points to consider on multiplicity issues in clinical trials, CPMP/EWP/908/99".<br><br>Proposed change (if any):<br>A significant benefit from co-primary endpoints of lung function and clinical symptoms should be demonstrated. | Accepted. |
| Lines 340-341 | 15 | Comments:<br>For specific immunotherapy other relevant phase II analyses could be environmental exposure chamber trials with measurements of symptoms or lung function, or a field trial with specific IgG4 as endpoint.<br><br>Proposed change (if any): | Partly accepted. Environmental exposure chamber is added, however IgG4 can only be used for pharmacodynamics, not for efficacy purposes. |
| Lines 364-366 | 15 | Comments:<br>This is exactly to the point. Comments given previously to duration of trials capturing asthma exacerbations relate to this very important issue that evaluation of immunotherapy must cover periods where the trial participants are exposed to allergen. | General comment previously addressed. |

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| | | Proposed change (if any): | |
| Lines 439 | 15 | Comments:<br>Please delete "number of" in the sentence "…, number of exacerbations or…" as it could as well be 'time to event' - that is a superior endpoint to 'numbers of' as it includes both time and numbers.<br><br>Proposed change (if any): | Accepted. |
| Lines 504 | 15 | Comments:<br>It would aid clinical development if age ranges were consistent across guidelines. Thus we suggest to align with e.g. CHMP/ICH/2711/99 and EMEA/CHMP/PEG/194810/2005: children: 2-11 years (may be subdivided into groups 2-5 years and 6-11 years) and adolescents: 12-18 years<br><br>Proposed change (if any): | Accepted |
| Lines 500-502 | 15 | Comments:<br>Please consider to reference the Paediatric Regulation (EC 1901/2006) for the requirement for commencement of the studies in children. The current wording does not allow for the application of deferrals, which is an option in the Paediatric Regulation.<br><br>Proposed change (if any): | Accepted |
| Lines 506- | 15 | Comments: | Text revised |

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| 508 | | It is not clear what the recommendation for paediatric population <5yrs really is.<br><br>Proposed change (if any): | |
| Lines 559 | 15 | Comments:<br>the reference to "lines 180-191" is not meaningful - should perhaps be 174-188?<br><br>Proposed change (if any): | Text revised |
| Lines 611-613 | 15 | Comments:<br>It is not clear what a "new biological treatment" is.<br><br>Proposed change (if any): | Text revised. |
| Lines 611-613 | 15 | Comments:<br>Is it implicit that relevant comparators exist? If so, why is it then required to demonstrate superiority and not equivalence? Please align with the ICH E10 guideline.<br><br>Proposed change (if any): | Text revised |
| Lines 611-613 | 15 | Comments:<br>It does not seem consistent to include children uncontrolled on low-dose ICS and not e.g. partly controlled on medium dose ICS? We suggest to elaborate/rewrite this sentence<br><br>Proposed change (if any): | Text revised |

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| Line 96-98 | 16 | The GINA Workshop Report classifies drug treatments as controllers or relievers. In addition **allergen immunotherapy (not as a controller or a reliever)** is available for allergic asthma although its specific role is not completely established yet**.**<br><br>**We may consider allergen immunotherapy as a therapeutic intervention that reduces allergen sensitivity (by inducing allergen tolerability) to the environmental factor, responsible for the asthma symptoms and asthma exacerbations, when exposure occurs.** | General comment already addressed in the guideline |
| Line 99-100 | | | Lines 99-100 accepted and text revised. |
| Line 102 | | Proposed text:…and include **anti-inflammatory drugs which control symptoms** (….) | Line 102 agreed |
| Line 152-154 | | …and **one** long-acting (**e.g.formotero**l) | Line 152-154 not accepted. Clinical guidelines are expected to be followed. |
| Line 163/4 | | The reversibility of FEV1 after inhalation of a short-acting β2 adrenergic agonist (**a few minutes after inhalation of 200-400 mcg of salbutamol or equivalent**) should normally be greater than 12-15% and 200mL **with respect to basal measurements**.<br><br>Patients randomised to study treatments should be | Line 163-4: accepted |

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| Line 165 | | **free from symptomatic/acute respiratory infection.** | Line 165 revised |
| Line 170 | | For clinical studies to investigate the efficacy of **allergen immunotherapy** the patients…. | Line 170: agreed |
| Line 174-176 | | …baseline **bronchial** eosinophilia, **measurement of exhaled nitric oxide** | Line 174-6: an adequate characterization of patients should be ensured in order to be included in CT. Reworded for more clarity |
| 207-208 | | In principle for a new product it is expected that separate studies are carried out for **each grade** of asthma severity for which the new product is intended to be used.<br>Comments: This is a problematic statement, since we know that asthma severity is very variable individually. | Line 207/208: text revised |
| Line 223 | | At inclusion of any survey, the patient may have a certain grade of severity and at the randomisation the severity may be changed. | Line 223: text revised |
| Line 249- | | **…known hypersensitivity** to NSAIDs status, eosinophilia, and<br>**sensitisations to** different **clinically relevant** allergens. | Line 249/251: revised |

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| 251<br><br><br><br>Line 308-311<br><br><br><br><br><br><br><br><br><br><br><br>Line 317<br><br><br><br><br><br><br><br>Line 340-341<br><br><br><br><br>Line 361 | | Whichever measure of airway obstruction is chosen the reproducibility and sensitivity of the method **should be assessed.**<br>Comments: EMA should indicate more specifically what type of reproducibility and sensitivity methods are requested (by EMA) for inclusion in this guideline.<br><br>Severe exacerbations of asthma are usually defined as a requirement for systemic corticosteroids **(oral or parenteral) and/or** a need for an emergency visit, or hospitalisation due to asthma.<br><br>However, to show the effects of **allergen** immunotherapy on the immune system, immunological changes (e.g. changes in allergen specific **IgE and IgG4 levels**, T-cell responses, and/or cytokine production) and/or modifications of end organ specific response (e.g. **allergen** provocation tests) **could be** measured. | Line 308-11: Not accepted. It is right that changes in allergen-specific IgG levels or bronchial reactivity cannot predict the level of clinical efficacy. However, this is not the issue for this kind of studies. This kind of studies should show a modification of the immune-system and thus the pharmacodynamics of the allergen product. And this is indeed possible. Since there are no other pharmacodynamics studies possible for this kind of therapy, such parameters should be measured. IgE may change, however it is not always changed, therefor it is not included.<br><br>Line 317: text revised<br><br>Line 340: The use of methacholine or histamine challenge is up to now very limited for allergen immunotherapy and knowledge about the usefulness is lacking. May be implemented later on if knowledge increases. Environmental exposure chamber included. |

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| | | Pharmacokinetic studies are **difficult to perform** for product for **allergen** immunotherapy. | Line 361: revised |
| Line 370-371 | | | Line 370: not accepted. We are referring to reliever medication |
| Line 386-387 | | For **allergen** immunotherapy bronchial provocation **tests (either non-specific (e.g. methacholine or histamine) or allergen-specific)** or reduction of controller medication may be considered for efficacy analysis.<br><br>**Allergen** Immunotherapy | Line 386-7: modified |
| Line 421 | | The preferred option is a three-arm study where the **new drug** is compared with placebo and with a short-acting β2 agonist | Line 421: text revised |
| Line 448 | | A third arm with a standard upgrading comparator should be considered. **The comparator(s) should correspond to the next medication step according to guidelines (i.e. increase in inhaled corticosteroid dose or adding a long acting** | Line 448: not considered needed |
| Line 467 | | | |

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| | | **bronchodilator to inhaled corticosteroids). However, in patients who are already receiving the optimal dose of inhaled corticosteroids associated with a long-acting bronchodilator, adding a third arm with monoclonal antibody-based therapies (i.e. anti-IgE, anti-cytokines) is not mandatory.** | Line 467: Not considered needed. This should be decide on a case by case basis and justified |
| Line 469 | | A new treatment should demonstrate achievement or maintenance of asthma control **and/or** reduction in exacerbations. | Line 469: Not accepted. The sentence compares inhaled therapy with systemic therapy meaning that inhaled therapy reduces the systemic exposure to treatment/drugs. It is not related to reduction of airway inflammation. |
| Line 505<br>Line 506-508 | | …biomarkers (**like FeNO, total eosinophils an**d other eosinophil markers) | No need to be so specific in a guideline<br>Accepted. Text revised |
| Line 510-511 | | Clinically significant interactions with commonly co-prescribed medications, particularly for the elderly, and with drugs relevant to the metabolic pathways of the new drug **should be studied**<br>Comments: This is a very broad concept. Needs to be more specific.<br>What will be the decision if not all drugs are studied or there is no evidence? Will the medication be approved? | Text revised to clarify this may be possible |
| Line 518 | | Inhaled therapy reduces the **airway inflammation** | Paediatric part fully reviewed and shortened |

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| Line 538<br><br>Line 572<br><br>Line 581 | | after systemic exposure and hence increases the margin of safety.<br><br>...in each age subset **(e.g. puberty).**<br><br>**Allergen** immunotherapy in children younger than 5 years **does not have clinical evidence and it is not recommended in daily clinical practice.** However since **allergen** immunotherapy has an indication for treatment of the paediatric population, products for **allergen** immunotherapy should be tested for efficacy and safety in paediatric populations.<br><br>**Children aged 5-11 and adolescents aged 12-17** can be investigated as a combined population. **Also, adolescents and adults can be combined**<br><br>**Add: "...history of food allergy"**<br><br>**Delete "vocal cord dysfunction"**<br><br>**Add : history of wheeze without airway infection** | |

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| | | **Add. Risk factors as parental asthma, atopic eczema and food allergy** | |
| Line 181 | 17 | Comments:<br>We consider that it is also important to note that patients' compliance to medication should also be evaluated before the start of the study. | Accepted. |
| Line 217-220 | 17 | Rationale and comment:<br>These lines needs to be updated to the opinion of CHMP concerning the time point on which FEV1 should be measured; On 15/07/2013 the CHMP (ORGAM) adopted the opinion that the prebronchodilator $FEV_1$ is influenced by the additional bronchodilator effect of a long acting $\beta_2$ agonist when it has not returned to its baseline. They also accepted the opinion that symptoms of a deterioration of inflammatory control can be masked by a long acting $\beta_2$ agonist. The ORGAM considered that the pre-bronchodilator FEV1 can be accepted as parameter to measure the anti-inflammatory effect provided by ICS, if the washout period of (long acting) bronchodilators is sufficient.<br><br>Short acting β2 agonists can be supplied to bridge the wash out period, provided that they are stopped 8 h before the lung function test.<br><br>Proposed change: "Pre-bronchodilator $FEV_1$ is | Accepted. Text modified although shortened not to be so explicit |

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| | | considered the most suitable variable and has been considered as a measure of asthma control. It can also be used to monitor the anti-inflammatory effect of inhaled corticosteroids, provided that the $FEV_1$ is not influenced by the concomitant use of bronchodilators. Therefore a sufficient washout period is needed i.e. the time that the $FEV_1$ returns to baseline. For the long acting bronchodilators formoterol and salmeterol a washout period ≥24 h is considered sufficient. For new (ultra) long acting bronchodilators the washout period needs to be determined in phase II studies. During the wash out period, short acting $\beta_2$ agonists can be supplied provided that they are stopped 8 hours before the lung function tests. The relationship between $FEV_1$ and symptoms experienced by patients is poor, but a low $FEV_1$ is described as an independent predictor of asthma exacerbations. “ | |
| Line 249-251 | 17 | Rationale:<br>This section is not clear. “The increase from the maintenance dose of corticosteroids” can be regarded as the increase of the maintenance *oral* dose corticosteroids or the increase of the maintenance *inhaled* corticosteroids.<br>Usually the use of oral corticosteroids is considered the treatment for a severe asthma exacerbation[1], while the (temporary) increase of maintenance dose of | Accepted |

[1] Redel et al. An official American Thoracic society/ European respiratory society statement: asthma control and exacerbations. Am J Respir Crit Care Med 2009; 180: 59-99

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| | | inhaled corticosteroids can be regarded as a treatment for a moderate asthma exacerbation.<br><br>Proposal: “Severe exacerbations are usually defined as the need of additional systemic corticosteroids for at least 3 days and/or a need for an emergency visit, or hospitalization due to asthma.” | |
| Line 422 | 17 | Rationale:<br>There are different definitions of asthma control. The advice is to define asthma control more specifically.<br><br>Proposed changes:<br>“A new treatment should demonstrate improvement or maintenance of lung function ($FEV_1$), symptom control, and reduction in exacerbations.”<br><br>A patient population that is sensitive to demonstrate a reduction in exacerbations is a patient population that had ≥ 1 exacerbations in the previous year. According to the current GINA guidelines, these patients are not well controlled and therapy should be intensified (i.e. standard treatment (line 378).<br>Therefore, a reduction in exacerbation will be difficult to demonstrate as the patients in the comparator arm might become too well controlled. | Partially accepted. Text revised for clarification |
| Line 317-319 | 17 | Currently, it is not possible to measure plasma concentrations of the immunotherapy. However, if | Accepted |

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| | | possible, plasma concentrations or the active substance should be measured.<br><br>Please change the wording to:<br>“The absence of pharmacokinetic studies for immunotherapy is accepted as long as it is not possible to measure the active substance. However, if possible, plasma concentrations should be measured.” | |
| Line 362 | 17 | Comments:<br>Clinical trials with immunotherapy should also be placebo controlled, to provide assay sensitivity due to the high placebo response.<br><br>Proposed change (if any):<br>“Clinical trials of products for specific immunotherapy should be parallel group, double blind, randomised and placebo controlled.” | Accepted |
| Line 432 | 17 | Comments:<br>Please add the word “ long acting” before bronchodilators in order to improve the readability.<br><br>Proposed change (if any):<br>“For a new long acting bronchodilators drug to be……” | Accepted |
| Line 439-440 | 17 | Comments:<br>An extensive list of primary endpoints for immunotherapy is provided. Please note that the study should be designed to evaluate the primary chosen | Not accepted. A short list of primary endpoints is provided regarding which endpoints could be used for immunotherapy. Up to know there is not enough knowledge to clearly dictate special endpoints. This is especially true for the mentioned |

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| | | endpoint.<br>Immunotherapy modifies the anti-inflammatory response of asthma. Therefore the study should include two co-primary endpoints, both a lung function parameter and an exacerbation parameter.<br><br>Proposed change (if any): | endpoints. It is known that often lung function (especially FEV1) is not impaired high enough to function as valuable endpoint. |
| Lines 531-554 | 17 | Comments:<br>The inclusion in the guideline of a listing with differential diagnosis for children with asthma is not recommended.<br><br>Proposed change (if any): | Text revised |
| Lines 154-155 | 18 | Comments:<br>We understand the term “medical history” to mean documentation required to be captured in the source records of a clinical trial.<br><br>Whilst clear guidance around the demonstration of $FEV_1$ reversibility with short-acting beta-agonist (SABA) is provided, acceptable methods and thresholds and/or other ways of demonstrating reversibility are not described.<br><br>$FEV_1$ reversibility to SABA is frequently performed in clinical trials, however, this is not standard practice in many centres and is not routine in primary care where | Accepted and modified<br><br>Not accepted. This should be in line with relevant guidelines.<br><br>Not accepted. Appropriate characterisation/identification of patients entering a clinical trial should be ensured. |

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| | | diagnoses are typically made and treatment initiated. More typical methods include response to ICS captured with PEF diaries or by $FEV_1$ between two visits (trial of anti-inflammatory therapy). As such, outside of specialist respiratory clinical trial centres, that may have historical documentation of reversibility, allowing eligibility based on the medical history may not result in the inclusion of a broader, “real world” asthma population unless allowance is made for how an asthma diagnosis is made in routine clinical practice.<br><br>Proposed change (if any): | |
| Lines 179-180 | 18 | Comments:<br>It is unclear what is intended by the statement “description in terms of minimum treatment received to maintain control is an important issue to be considered”. Additional information regarding the expectation as to how these data will be used, will assist sponsors in ensuring that all relevant information is collected, where available. For studies in patients who are uncontrolled at screening (e.g. on an inhaled corticosteroid alone), unless they have recently been stepped down it will not be possible to know what the minimum treatment to attain control would be as the patients are, by definition, “uncontrolled”. For patients who are currently controlled it may not be possible to know what the minimum treatment they | Text revised. The intention is to avoid overtreatment of patients by ensuring adequate treatment to ensure control. Otherwise, interpretation of study results might be biased. |

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| | | would require to maintain control without stepping them down.<br><br>In the majority of cases it is unlikely that medical records will allow such determinations to be made. In addition, given the variable nature of the disease it will be difficult to draw firm conclusions from historical data, even if available (e.g., the minimum level of therapeutic intervention required to maintain control may not have been the same 9 months previously).<br><br>Proposed change (if any): | Not accepted. It will depend on the studied population. |
| Line 183 | 18 | Comments:<br>The statement “previous history of exacerbations should be well-documented”, should clarify whether this refers to moderate or severe exacerbations. It may be difficult to capture previous ‘moderate’ episodes and distinguish treatment changes made for poor asthma control *versus* a moderate exacerbation.<br><br>It would also be helpful to define a minimum timeframe prior to screening, over which this data is expected to be collected (e.g. 6 months, 12 months or 24 months). | Not accepted. See previous comment |

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| Lines 249-256 | 18 | The guidelines reflect the asthma exacerbation definitions suggested by the ATS/ERS taskforce. It is unclear how sponsors should define events where patients receive short-term treatment with systemic steroids (e.g. oral prednisolone for 2 days), which meets neither the definition of a moderate nor a severe exacerbation. Inclusion of a standardised approach to this situation may be of benefit to sponsors and ensure consistency.<br><br>Proposed change (if any): | Text revised accordingly. |
| Line 263-264 | 18 | Comments:<br>The requirement to document the season during which exacerbations and wheezing episodes occur implies that they will be required for analysis. Is this requirement in the context of specific immunotherapy for all studies where asthma exacerbations are the primary endpoint? Clarification is required concerning how these data will be used to enable sponsors to collect all of the data that may be required to undertake analyses around this. Seasons defined by "traditional months" are of limited utility as they will vary from region to region (northern hemisphere *versus* equatorial, *versus* southern hemisphere) and the meteorological aspects associated with seasons are highly variable from year to year. In studies of seasonal allergens, the true pollen season is required | Text revised. |

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| | | to define the study rather than just the month, although we note that these are not the cause of the majority of asthma exacerbations.<br><br>Whilst there is clustering of viral triggers in autumn and winter, these are not consistent from year to year. Patients may have specific seasonal allergens in addition to the typical perennial asthma allergens; unless all patients have skin prick tests routinely, as an additional procedure, it is not clear how these data could be interpreted.<br>Additional information regarding how the data will be used will be of value to sponsors.<br><br>Proposed change (if any): | |
| Line 288 | 18 | Comments:<br>The terminology “no control” is inconsistent with the language used elsewhere in the document, which refers to the GINA definitions of controlled asthma, partially controlled asthma and uncontrolled asthma.<br><br>Proposed change (if any): | Text revised. Accepted. |

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| Lines 359-360 | 18 | Comments:<br>ICS are described as the “comparator of choice” for studies of controller medication. This should be clarified to reflect this is in the context of new first line controller therapies. ICS alone would not be the comparator of choice for studies of many patients at GINA steps three to five.<br><br>Proposed change (if any): | Accepted. Text revised. |
| Line 375 | 18 | Comments:<br>The use of the word “milder” is inconsistent with other text within the document which notes the move away from such terminology in the treatment guidelines and a focus on control and treatment to define patients. To avoid confusion caused by potentially different interpretations of the word “milder”, patients could be better described according to GINA step or by medication (e.g. treatment naive or low dose ICS).<br><br>Proposed change (if any): | According to GINA 2014, this term is recognised as a step forward classification of patients. |
| Line 394 | 18 | Comments:<br>It is unclear how to interpret the term “standardise” and whether this refers to one specific product, or to one class of treatments (e.g. mid-dose ICS/LABA). The recommendation to standardise concomitant asthma medication may reduce aspects of data variability and may be appropriate for some studies but may not for | Text modified slightly to allow flexibility but the main message remains. |

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| | | many others, especially studies of add-on therapies. However, this may not reflect the range of treatments or combinations of treatment that patients may be on within a single GINA step (e.g. GINA step 4). It may not be reflective of how a drug will be used in clinical practice and will likely result in step-down of some patients, or stepping some patients back to treatments or doses that have previously proven ineffective or were poorly tolerated.<br><br>Proposed change (if any): | |
| Line 457 | 18 | Comments:<br>Is the statement “long-term safety data from at least 1 year of treatment should be provided”, intended to apply to both reliever medications and controller medications, or controller medications only? This should be clarified.<br><br>Proposed change (if any): | Accepted. It applies to controllers |
| Line 544 – 554 | 18 | Comments:<br>Please consider inclusion of this information into the Section dealing with children of 6 years and older (Lines 514-523), as many of these points apply also to older children<br><br>Proposed change (if any): | Text revised |

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| Line 583 | 18 | Comments:<br>The importance of generating data in children is appreciated, however, we also recognise that it is challenging to recruit patients aged under six years and exceptionally hard to recruit patients aged less than two years. We would suggest simplifying the requirement for the window of one episode to be within 6 months prior to enrolment rather than the narrow window of 3-6 months currently proposed, to improve the ability to identify and recruit patients in this age range within a reasonable time frame.<br><br>If the intention is to ensure that unstable patients are not recruited the current text would not prevent patients who had experienced a more recent event (e.g. 2 weeks previously), as long as a wheezing event was within the proposed window. We would suggest that the responsibility for defining a minimum recovery period between a wheezing event and screening be defined by individual sponsors in the protocol, as appropriate.<br><br>Proposed change (if any): | Text revised allowing some flexibility. Importance of adhering to clinical guidelines for diagnosis. |

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| Line 597-598 | 18 | Comments:<br>It should be clarified if the classification of severity of asthma exacerbation in Section 4.2 is also intended to be applied to children aged younger than 6 years. We note the use of the term “wheeze exacerbations”, on line 598 which is not a standard adult term or included in Section 4.2. We would not expect the definition or clinical approach to exacerbations in children aged younger than 6 years to be the same as that undertaken for adults. | |
| Lines 611-613 | 18 | Comments:<br>The requirement to study new biological treatments in children aged 6 years and older as an add-on to low-dose ICS is not typical of where these agents are intended for use (e.g. as add-on therapy to mid-dose ICS/LABA), or how they may be used in clinical practice. We assume that the reference to low-dose ICS reflects the paediatric steroid potencies outlined in GINA (Figure 3.4 estimated equipotent daily doses of inhaled glucocorticosteroids for children older than 5 years), meaning that patients would be evaluated with biological agents if uncontrolled on doses as low as beclomethasone 100mcg total daily dose. We would anticipate many parents and investigators being very reluctant to take this approach and evaluate biological treatments in patients at GINA step II. | Text fully revised. Study design, including studied population, background medication, and comparator, is mainly based on severity of asthma |

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| | | Proposed change (if any):<br>We would propose recommending that studies requiring use of an appropriate and justified active comparator should be undertaken, without specifying products or doses. | |
| Lines 621 – 626 | 18 | Comments:<br>As the corresponding text for the adult population provide a clear minimum requirement for long term safety data, i.e. at least 1 year of treatment, similarly it would be useful to provide guidance regarding the long term safety data required for the paediatric population.<br>Proposed change (if any): | Text revised |
| Lines 653-655 | 18 | Comments:<br>The current text may benefit from clarification. The rationale behind this statement is clear, although we would suggest that the overriding consideration must be provision of a rescue medication that an individual child and caregiver can reliably use, especially given clinical features potentially associated with a requirement for rescue medication (tachypnoea, anxiety, difficulty in taking deep inspiration).<br><br>We would not encourage a situation where protocols for DPI products encouraged investigators to change a patient to a DPI to meet this recommendation if an individual child was more familiar with MDI and spacer. | Text fully revised |

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| | | Proposed change (if any): | |
| Lines 658-659 | 18 | Comments:<br>It should be clarified if the requirement to demonstrate this applies to all inhaled devices including those of background and rescue medications. The requirement may have implications for manufacture and supply of dummy devices if visit windows do not always coincide with treatment windows. Patients handling a device (e.g. priming) may share devices, however practice inspiratory manoeuvres are usually patient specific which will require additional supplies and plans for storage of dummy devices by the patient or site.<br><br>Rescue medication is frequently sourced locally from commercial supplies within the country and dummy devices may not be available.<br><br>Proposed change (if any): | Text revised |
| | 19 | EMA-Asthma_comme | REPEATED. Already revised. |
| Line 323 | 20 | Comments:<br>It is not entirely clear what is meant by "*the crucial part of the dose-response curve*". It would be helpful if this matter was explained, e.g. by stating what parameters should be considered when selecting which part of the dose-response curve is crucial.<br><br>Proposed change (if any): | Text modified to clarify that the total curve should be characterised. |

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| Line 375 | 20 | Comments:<br>The use of "*milder patients*" could be confusing, as it associates with the old classification of asthma. It is recommended to delete the word "milder" from the text. Proposed change:<br>"*With the exception of ~~milder~~ patients, for whom no controller treatment is currently recommended (…)*"<br><br>Proposed change (if any): | Not accepted. See recently updated GINA 2014 |
| Lines 426-428 | 20 | Comments:<br>Similarly as in the comment above, in view of the new classification of asthma, the use of "*(…) in mild asthma*" can be confusing. It is recommended to rephrase this sentence taking into account the new asthma classification.<br><br>Proposed change (if any): | Not accepted. See above |
| Lines 504-505 | 20 | Comments:<br>It would be helpful if the guideline explained in more detailed what is considered as "*well defined population of children (…) in each age subset*". Should the size of this population be estimated taking into account statistical aspects?<br><br>Proposed change (if any): | Text modified and clarified |
| 83 | 21 | Comments:<br>It would seem appropriate to reference the most | Accepted to include GINA 2014 |

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| | | recent version of the GINA guidelines (2012).<br><br>Proposed text change:<br>(NHLBI, 2007; GINA, 2012).<br><br>Proposed change (if any): | |
| 99 | 21 | Comments:<br>Long-acting β agonists are missing from the list of controller medication.<br><br>Proposed change (if any):<br>Controllers are taken daily and long-term and include both anti-inflammatory drugs and drugs which control symptoms (inhaled corticosteroids, long-acting β agonists, leukotriene modifiers, anti-IgE treatment, oral corticosteroids). | Accepted. Text revised. |
| 153 | 21 | Comments:<br>The reversibility criteria suggested at 12-15% is not consistent with most International guidelines for the diagnosis of asthma, e.g. GINA 2012 which suggests ≥12% and 200 mL improvement in $FEV_1$. A reversibility of 15% would be relevant to identify a highly reversible population of subjects in order to increase the treatment effect of a bronchodilator and thus reduce the sample size of a study but for the general purpose of diagnosis of asthma for most clinical studies the GINA definition is more appropriate. | Accepted. Text revised. |

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| | | Proposed change (if any):<br>The reversibility of FEV1 after inhalation of a short-acting β2 adrenergic agonist should normally be ≥12% % and 200 mL. | |
| 174-178 | 21 | Comments:<br>To be consistent with GINA descriptors, we would recommend not using the term “severity” in isolation but rather intensity of treatment and controlled, partly controlled or uncontrolled to classify asthma.<br><br>Proposed change (if any):<br>The risk posed by asthma depends upon its severity. Asthma severity is classified on the basis of the intensity of treatment required to achieve good asthma control. In principle for a new product it is expected that separate studies are carried out for each grade of asthma severity for which the new product is intended to be used. The criteria used to classify the intensity of treatment and the degree of asthma control achieved using a specified therapeutic regime (controlled, partly controlled, uncontrolled) should be clearly established in the protocol as the current clinical classification differs from that stated previously in treatment guidelines. | It is crucial that the studied population is well characterised with according to the pertinent clinical guidelines. |
| 244-264 | 21 | Comments:<br>The definitions/descriptions of asthma exacerbations in | Text modified to ensure that generally accepted definitions based on relevant EU/international guidelines are used. |

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| | | particular regarding severity are not consistent with those described in GINA 2012. In order to ensure that guidance for development of new drugs is consistent with currently accepted treatment guidance, it would be advisable to be consistent with GINA 2012. The proposed severity descriptors of exacerbations in the document are simplified and would likely lead to over reporting of severe exacerbations if patients are treated with systemic corticosteroids or increased dose of inhaled corticosteroids.<br><br>Mylan recommends consistency with GINA 2012 definitions for severity of exacerbations.<br><br>Proposed change (if any):<br>The following definitions for exacerbations should be considered:<br><br>Severe exacerbations of asthma are characterised by breathlessness, loud wheezing and acute shortness of breath at rest. Agitation, difficulty speaking, respiratory distress (respiratory rate > 30/ minute, pulse rate >120), with visible signs of chest tightness and cyanosis are often noted. They are life-threatening episodes with a reduction in peak flow of more than 40% predicted following bronchodilator treatment and hospitalization due to asthma. | |

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| | | Treatment would usually be with corticosteroids (inhaled, oral or systemic [IV or IM]).<br><br>Moderate exacerbations are usually considered as events that require a change in treatment to avoid progression of worsening asthma to a severe exacerbation and the occurrence of one or more of the following – deterioration of symptoms of asthma, increased use of “rescue” inhaled bronchodilators, deterioration in lung function (peak flow reduction 20 to 40% predicted), which lasts for two days or more but may not be severe enough to warrant hospitalization. Moderate exacerbations may be treated with corticosteroids (inhaled, oral or systemic [IV or IM]).<br><br>Milder exacerbations are defined by a reduction in peak flow of less than 20% predicted, nocturnal awakening , increased use of β agonists, and can be difficult to differentiate from the normal variation seen in some cases of asthma control. Mild exacerbations may still be treated with increased doses of corticosteroid (inhaled or oral). | |
| 261-264 | 21 | Comments:<br>It is not clear what is meant by “The length of the study… and as recruitment should continue throughout all four seasons a twelve-month follow-up is a | Text clarified. |

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| | | minimum requirement."<br>If a study recruits rapidly, the recruitment period may not be throughout all 4 seasons, the treatment period would of course be over all seasons if the treatment duration is 12 months. It is also not clear what is meant by a 12 month follow up period; does this mean safety follow up of 12 months beyond the 12 month treatment period?<br><br>Proposed change (if any):<br>This paragraph should be updated to ensure clarity. | |
| 288 | 21 | Comments:<br>For validated composite measures e.g. ACQ, we are assuming that further validation is not required for each individual development programme or study.<br><br>Proposed change (if any): | This is self-evident. |
| 325 | 21 | Comments:<br>Mylan recommends stating that placebo and an active control are "recommended" rather than "needed" as needed suggests an active control is mandatory.<br><br>Proposed change (if any):<br>Alternatively, to enhance the assay sensitivity the inclusion of a placebo and/or an active control would be recommended. | Text modified. |
| 331 | 21 | Comments: | Text modified. Accepted. |

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| | | If the comparator is well characterised, the use of one dose of comparator should be valid and therefore, two doses of the comparator should not be required. In the case of some comparators, there may be only one dose of the comparator approved or the dose response is unlikely to be observed without very large sample size e.g. ICS; in this case, it would not be appropriate to include 2 doses of comparator in an exploratory dose response study.<br><br>Proposed change (if any):<br>For β2 adrenergic agonists, a cumulative dose response may be performed preferably using FEV1 (or peak expiratory flow) as a pharmacodynamic endpoint; for anti-inflammatory drugs parallel group comparative studies are likely to be necessary comparing at least two, if not, more doses of the test drug with one or more doses of the comparator drug. | |
| 336-338 | 21 | Comments:<br>It is unclear why the duration of study for long-acting bronchodilators is recommended to be 6-12 weeks for dose response studies. The primary endpoint for these studies would likely be $FEV_1$ or other related lung function measures for which the maximal effect can ordinarily be observed within 2 weeks of dosing so additional dosing would seem unnecessary. | The guideline suggest this as an example but final decision will be decided on a case by case based on MoA, endpoints, etc. Text modified. |

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| | | Likewise for some anti-inflammatory agents, e.g. ICS the maximal effect on $FEV_1$ can be observed within ~4 weeks of dosing so dosing greater than this would seem inappropriate.<br><br>Proposed change (if any):<br>We would suggest that the duration of studies is amended to state that it should reflect the pharmacology and individual characteristics of the drug and proposed endpoints rather than stating specific values here which would seem rather too long for exploratory studies.<br><br>Proposed text change:<br>The duration of studies, should reflect the pharmacology and individual characteristics, such as mechanism of action, of the drug and the selected endpoints. | |
| 357 | 21 | Comments:<br>In order to facilitate global registration programmes and to lessen the risk of reduced access to medicines for asthma, it would be optimal if EU guidance could be consistent with FDA guidance in terms of duration of pivotal studies for efficacy. A study of 3 months duration is sufficient to demonstrate efficacy across the range of asthma controller medicines (e.g. inhaled corticosteroids, long-acting beta agonists, leukotriene | Text modified. Accepted. |

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| | | antagonists and anti-IgE therapy) with the majority of endpoints. Whilst longer studies (i.e. 6 months to 1 year) may be required for specific claims relating to prevention of exacerbations, 3 month studies are sufficient for the majority of other endpoints to show maximal clinical benefit. Furthermore, as there is no evidence of tachyphylaxis with any asthma controller medication studies of 3 months duration would seem appropriate to show maintenance of therapeutic benefit for controller medications, particularly for new entrants in established classes of medication e.g. novel ICS.<br><br>Proposed change (if any):<br>Claims for chronic treatment with controller medication should be supported by the results from randomised, double blind, parallel group, controlled clinical trials of at least three months duration, although a longer duration may be necessary depending on the endpoint selected (for example, exacerbations). | |
| 404 | 21 | Comments:<br>It is unclear why an independent adjudicating committee be recommended to assess efficacy endpoints if the primary endpoint is likely to be $FEV_1$. With centralised spirometry in place, independent review and quality control of spirometry data can be | Text revised. |

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| | | readily performed.<br><br>An independent adjudication committee may be appropriate for assessment of exacerbations, but if these are clearly defined in the protocol, an independent adjudicating committee would not be needed.<br><br>Proposed change (if any): | |
| 421 | 21 | Comments:<br>It is unclear why it would be necessary to show both a reduction in exacerbations and improvement in asthma control for new controller medications. One of these endpoints in addition to changes in lung function e.g. $FEV_1$ would seem appropriate prior to registration. This would reduce the need to perform large expensive exacerbation based studies prior to registration which could be a barrier to the development of novel agents.<br><br>Proposed change (if any):<br>A new treatment should demonstrate achievement or maintenance of asthma control or reduction in exacerbations. In addition, for a new controller treatment, equal emphasis should be placed on lung function and symptom based clinical endpoints. | Text modified for clarity. |
| 519-523 | 21 | Comments: | Text revised |

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| | | We would be interested to understand the reference from which the statement "As the most frequently used inclusion criteria, i.e. >12% improvement in $FEV_1$ etc." is taken from as this is not taken from GINA 2012 to justify why a 10% value for reversibility or $PC_{10}$ for induced bronchoconstriction would be selected.<br><br>Proposed change (if any): | |
| 559 | 21 | Comments:<br>It is not clear what is being referenced in section 4.1 (lines 180-191).<br><br>Proposed change (if any): | Text revised |
| 564-565 | 21 | Comments:<br>We would be interested to understand the reference from which the justification can be made for selection of a 10% value for reversibility or $PC_{10}$ for induced bronchoconstriction. We agree and acknowledge that achieving 12% reversibility is challenging in paediatric patients but the 10% value is not in GINA guidelines and would appear somewhat arbitrary.<br><br>Proposed change (if any): | Accepted. Text completely revised. |
| 579 | 21 | Comments:<br>Why would the episode have to occur within 6 months of enrolment? If the subject had prior events and since then it has been well managed on maintenance | Accepted. Text revised |

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| | | therapy, they may not have had episodes within the 6 months prior to enrolment in the study. This restriction would potentially raise an unnecessary hurdle to recruitment into clinical studies.<br><br>Proposed change (if any): | |
| 583 | 21 | Comments:<br>Why would the episode have to occur within 3-6 months of enrolment? If the subject had prior events and since then has been well managed on maintenance therapy they may not have had episodes within the 3-6 months prior to enrolment in the study. This restriction would potentially raise an unnecessary hurdle to recruitment into clinical studies.<br><br>Proposed text change:<br>……one of these episodes needs to be doctor confirmed. | Accepted. Text revised |
| 600 | 21 | Comments:<br>The paediatric ACQ has only been validated in patients >6 years of age (http://www.qoltech.co.uk/acq.html) so would not be appropriate to state in the guidance document that it is appropriate for use and has been validated in patients <6 years of age.<br><br>Proposed change (if any): | Text revised |

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| 611-619 | 21 | Comments:<br>Is it ethically appropriate to conduct placebo controlled studies in paediatric asthmatic patients? Where good, well established products have been available for paediatric use for many years, it would seem more appropriate to perform 2 arm studies vs. SoC or another comparator.<br><br>Proposed change (if any): | Text revised<br>Accepted. Explanation added to the text:<br>“Placebo controlled trials are possible if adequate rescue medication is available. Active controls are especially valuable in the lower grades of severity, as there are established treatment regimens (e.g. addition of LABAs if patient is uncontrolled on ICS).”<br>……..<br>“In higher grades of severity, study drugs are added to standard therapy and not administered as mono-therapy. In this case a placebo-controlled trial with add-on design (standard therapy +study drug versus standard therapy +placebo) with adequate rescue medication would be the preferred design.” |
| 634-664 | 21 | Comments:<br>It is a generalisation that for children under 6 years of age, therapy should be via pMDI and spacer and that where this is not effective, could consider nebulised therapy, thus assuming that children under 6 years are unable to use DPIs. There are published papers (Kamps *et al*,Pediatric Pulmonology 37:65–70 (2004), Nielsen *et al*, Eur Respir J 1998; 11: 350–354, Bisgaard *et al* Eur Respir J 1998; 11: 1111–1115) showing that children >4 years of age are capable of generating the minimum inspiratory flow through marketed DPIs in order to deliver a dose and a number | Although most spacers are product-specific there are also universal spacers that could be used with different inhalers. The important point here is that spacers should also be age-specific, taking account of specific needs, e.g. use of facemask below 3 years of age or use of dry powder inhaler (DPI) at the age when children can generate active inhalation as compared to passive inhalation with pressurised metered-dose inhaler (pMDI). |

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| | | of products are approved for use in paediatric patients.<br><br>Whilst it is true that the airflow resistance varies greatly between DPIs and that the flow rate required to deliver a dose will also vary between devices, children >4 years can still use DPIs. It is relatively easy to check if a child is a suitable candidate for using a particular DPI as commercially available flow meters like the In-Check Dial (http://www.clement-clarke.com/ProductInfo/InhalerTechniqueTraining/InCheckDIAL.aspx) can be used to assess the peak inhaled flow that a child could generate through a range of marketed DPIs by simulating the air flow resistance of these devices.<br>Provided the child can generate a satisfactory flow rate through the DPI, it may be preferable/more reliable to deliver the drug via the DPI then expecting a child <6years to inhale the dose from a nebuliser via tidal breathing (likely to be 5-10 minutes administration time).<br><br>Proposed text change:<br>Particular attention should be paid to the effects of age on the adequate function of inhalation delivery devices. The choice of device should be governed by individual need and the likelihood of compliance. | |

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| 643 | 21 | Comments:<br>It is not clear what is referenced by non-pressurized MDIs. Does this refer to soft mist inhalers and nebulisers?<br><br>Proposed change (if any): | This is generally accepted terminology. No changes needed |