Pragmatic RCT of high-dose oral montelukast for moderate and severe pediatric acute asthma exacerbations

Clinical Protocol Synopsis

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Version 1.0
September 27, 2017

Focus of the study: To improve outcomes for children with acute asthma exacerbations.

Objectives of the study: To determine the extent to which high-dose (30mg) oral montelukast, added to standard treatment in children with moderate and severe acute exacerbations (1) Rapidly improves lung function and clinical severity; and (2) Decreases hospitalizations and 72-hour symptom burden.

Central Hypothesis: High-dose oral montelukast, added to standard treatment in children aged 5 – 17 years with moderate and severe acute asthma exacerbations, rapidly improves lung function and clinical severity and decreases hospitalizations and 72-hour symptom burden.

Secondary Hypotheses:  
1) There are greater effects of high-dose oral montelukast on lung function and on our secondary outcomes with respiratory viral detection or leukotriene-mediated inflammation; and  
2) There is an interaction between viral detection and urinary LTE4 level with treatment-response.

Study Design: A two-arm, parallel randomized controlled trial of high-dose oral montelukast versus identical placebo, as add-on to standard treatment of systemic corticosteroid (SCS) and inhaled short-acting β2-agonist (SABA), in children aged 5 – 17 years with moderate and severe acute asthma exacerbations.

Intervention to be tested: High-dose oral montelukast added to standard treatment as one treatment-allocation arm, in comparison with standard treatment as the 2nd treatment-allocation arm.

Primary and Important Secondary Endpoints: For our Primary Aim, the primary outcome measure to be compared between arms will be change of %-predicted airway resistance at 5Hz (%R5) by impulse oscillometry (IOS) at 2-hours after treatment initiation. Secondary outcomes will include improvement of %-predicted FEV1, clinical severity measured using the validated Acute Asthma Intensity Research Score (AAIRS), hospitalization rate, and 72-hour symptom burden using the Pediatric Asthma Caregiver Diary (PACD). For our Secondary Aim, we will determine (1) The effects of high-dose oral montelukast on lung function and on our secondary outcomes in the presence of nasal viruses and of greater leukotriene-mediated inflammation; and (2) The degree of interaction between viral detection and urinary LTE4 level with treatment-response.
Schedule of clinical and laboratory evaluations: The primary outcome (change of %R5) and select secondary outcomes (%FEV1, AAIRS, LTE4) will be measured before and again at 2-hours after treatment initiation. The other secondary outcomes will be measured at the time of hospitalization decision-making by the clinical team (hospitalization rate) or at 72-hours after treatment initiation (PACD).

Study Population and Sample Size

Study population: Inclusion criteria are children aged 5 – 17 years of both genders; parental report of an asthma diagnosis by a health care provider and at least one previous wheezing episode treated with albuterol; presenting to our tertiary, urban children’s hospital emergency department (ED) in middle Tennessee comprised of urban, suburban and rural subpopulations; and with moderate or severe acute asthma exacerbation measured using the AAIRS bedside asthma severity score. Exclusion criteria include prior study enrollment; chronic lung disease other than asthma; history of prematurity less than 34 weeks’ gestational age; acute or chronic liver disease; presence of tracheostomy; use of noninvasive ventilation at home; need for immediate airway intervention (e.g., endotracheal intubation or noninvasive ventilation); allergy to montelukast; pregnancy; tuberculosis; gastroesophageal reflux requiring acid-blocking medication; and use of leukotriene-modifying medication.

Sample size: As noted below, we will enroll 330 participants with 165 randomized to each arm.

Statistical Design and Power

Primary statistical inferential test: Outcomes are measured on a continuous scale and will be analyzed using linear regression and include treatment indicator and baseline value as covariates. We will estimate the bias corrected mean effect of treatment with corresponding 95% confidence intervals that taken into account one planned interim analyses. We will ascertain that the assumptions of inferential tests are satisfied for all analyses. If assumptions are violated, alternatively we will use the proportional odds ordinal logistic regression model which generalizes the non-parametric Wilcoxon rank sum test to a regression setting.

Expected effect size: We expect that high-dose montelukast will result in a minimum 15% greater improvement in %R5 and a 10% improvement of %FEV1 between pre-treatment and 2-hours after dosing in comparison with standard treatment.

Secondary tests for effect modification by LTE4 level and viral detection. As noted in section C.5.b. above, we anticipate an interaction of montelukast with urinary LTE4 levels and viral detection. Additional subgroup analyses by age groups, pretreatment severity (moderate versus severe) and rapid response (10 minute) to albuterol are also of interest. To test secondary hypotheses that the treatment effect is modified by covariates, we will fit separate models that also include the interaction of the covariate with the treatment effect. Using the sample size assumptions above and additionally anticipating that 60% to 80% of subjects will have viral detection at baseline, we have 80% power to detect a 25% to 31% modification of the treatment effect. We will report the results of all subgroup analyses conducted regardless of statistical significance.

Intention-to-treat-analysis and inferential test assumptions: Analyses will conform to the principle of intention-to-treat. All randomized participants will be included in the primary and secondary analyses in their assigned treatment allocation groups.

Power calculation: The primary outcome measure will be %R5 because this IOS parameter measures total airway resistance. Our data from 192 children aged 5 – 17 years with acute asthma exacerbations include an SD for pre-treatment %R5 of 71.7% and a correlation coefficient (r) of 0.52 between pre-treatment and 2-hour %R5. For residual variance we considered a linear regression model with the 2-hour value as the outcome and the pre-treatment value as an adjustment variable. With 125 participants having complete IOS data in each of the two treatment-allocations arms, we will have 90% power to detect a minimal difference of %R5 of 14% between montelukast and placebo with one interim data analysis conducted when 50% of the subjects have accrued. In order to account for missing IOS data in up to 15% of participants, dropouts and missing data we propose to enroll 330 participants with 165 randomized to each RCT arm.

We will also examine additional IOS parameters as outcomes, including those representing large (R20) and small airway function (R5 – R20, X5 and XA), as well as change of %-predicted FEV1 (%FEV1) and of the AAIRS bedside severity score between pre-treatment and 2-hours. Because we anticipate that approximately 50% of our cohort with moderate and severe exacerbations will be able to provide spirometry meeting ATS quality and reproducibility criteria, there may be insufficient power to detect meaningful differences for this outcome. However, we will be able to score the AAIRS in all participants and thus anticipate sufficient power to
detect a minimum 2-point difference of this 17-point severity score between montelukast and placebo arms.

**Stopping rules for use by the Data Safety and Monitoring Committee**
Stopping boundaries and design operating characteristics were investigated using the RCT-design R package. This package provides a comprehensive suite of functions for evaluating, monitoring, analyzing, and reporting adaptive clinical trial designs. While finalized stopping rules will be developed and agreed on by investigators during the R61 startup phase, we summarize some current results. Using the Emerson and Flemming (1989) symmetric test with an assumed treatment effect of 14% and standard deviation of 34%, we would stop the trial early at the interim analysis for futility if estimated treatment effect is 0.0% or lower and stop early for efficacy if the treatment effect is 17.0% or greater. If the true treatment effect is 14%, there is an estimated 32% chance of stopping early. Should the trial continue to full enrollment, the bias adjusted treatment effect will be significant for efficacy if it is estimated to be 8.5% or larger.

**Missing data will be handled by joint modeling of the treatment effect and informative missing data.**
We expect that outcome data on some subjects will be missing, and this data will not be missing (completely) at random. In particular, FEV₁ measurements will be more difficult to obtain on subjects with more severe exacerbations. Failing to account for the informative missingness could bias the estimate of the treatment effect, so we will consider joint models for the missing data and estimated treatment effect [Fitzmaurice, in Roy]. Sensitivity analyses in which the treatment is estimated using different models for the missing data will be conducted to determine the robustness of the treatment effect estimate. Detailed analyses plan that specify the missing data models will be created before data collection, during the R61 startup phase.

**Group Assignment**

**Drug preparation:** The Vanderbilt Investigational Drug Service will prepare randomized treatment packs of active drug (montelukast, 30mg) and identical placebo, numbered sequentially by subject ID and identical in appearance except for bar coding on the outside of the pack. Treatment packs will be inventoried in the locked, secure ED research refrigerator. Participants will also be provided montelukast 5mg chewable or identical placebo with instructions to administer one daily for 3 days.

**Randomization:** We will use randomly-permuted blocks of 4 to 8 to minimize seasonal bias of exacerbation precipitants that may have independent associations with treatment-response. The study biostatistician will use randomization software to provide a randomization schema to the Vanderbilt Investigational Drug Service.

**Masking of treatment-allocation and outcome-ascertainment:** Investigator or clinical team knowledge of treatment allocation may influence assessment of outcomes. Allocation concealment will minimize this bias. We will adhere to established procedures to maintain masking of participants, CTAs, and data analysts.

**Subject Participation Duration:** Individual participants will complete study participation after completion of the PACD symptom diary at 72-hours after treatment initiation.

**Study Duration:** As presented in the Milestone and Timeline Figure (next page), completion of data collection will be after the 3rd quarter, year 4 of initiation of the R61 planning award. Final data analysis will be complete after the 4th quarter, year 5.
### Milestone timeline for Bi-phasis R61 (planning) and R33 (RCT execution)

<table>
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<tr>
<th>R66 Start-up Phase</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
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<td>DSMB formation + NHLBI/IRB approval</td>
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<td>Recruit + train CTA, study coordinator</td>
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<td>Equipment + drug acquisition</td>
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<td>Educate ED team on protocol</td>
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<td>RCT enrollment</td>
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<td>Progress report, NHLBI review</td>
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| R33 Full-enrollment and Clinical Trial Execution Phase                           |        |        |        |        |        |
| RCT enrollment                                                                   |        |        |        |        |        |
| Viral PCR, LTE₄ assays                                                          |        |        |        |        |        |
| Data cleaning and database lock                                                  |        |        |        |        |        |
| Data analysis, manuscript preparation                                            |        |        |        |        |        |
| Submit results to ClinicalTrials.gov                                            |        |        |        |        |        |

Abbreviations: CTA, clinical trials associate; IDS, Investigational Drug Service; LTE₄, leukotriene E4;
1. FDA IND (#136451) and clinicaltrials.gov registration (NCT03277170) completed September, 2017.
2. Laboratory plan will include Vanderbilt Eicosanoid Core laboratory and Halasa lab (viral studies).
3. Consent / Assent documents and CRFs will be developed within the REDCap electronic Consent and CRF system to enable direct electronic data entry at the bedside.
4. Per PAR-16-405, RCT enrollment begins with R61. NIH administrative review will determine whether milestones are met and whether the R33 phase award will be issued, subject to funding availability.

### References