4.0 Abstract

Title:

A study of growth, development and maturation in adolescents with atopic dermatitis who receive upadacitinib

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Rationale and Background:

Atopic dermatitis (AD) is a common chronic relapsing inflammatory skin disease. The prevalence of AD is much higher in children than in adults.[1] Upadacitinib is an oral selective and reversible inhibitor of Janus kinase (JAK) that is approved by the European Medicines Agency (EMA) for the treatment of moderate to severe AD in adults and adolescents 12 years of age and older who are candidates for systemic therapy. The JAK/signal transducer and activator of transcription (STAT) pathway is involved in the downstream signaling of inflammatory cytokines, multiple growth factors, and bone remodeling.[2,3] Patients with AD have multiple potential risk factors for decreased bone mineral density, osteoporosis, and fracture risk.[2,4] The available preclinical and clinical data for upadacitinib do not suggest a risk associated with bone development and maturation in patients ≥ 12 years old. However, the long-term use of upadacitinib on growth and maturation in adolescents is not known; thus, it is important to gain knowledge of these and characterize growth and development in adolescents who receive upadacitinib. This study will evaluate growth, development and maturation in adolescents who receive upadacitinib for treatment of moderate to severe AD versus other systemic treatments.

Research Question and Objectives:

This study aims to evaluate the growth, development and maturation in North American (US and Canada) [NA]-residing adolescents with moderate to severe AD who receive upadacitinib versus biologic or other non-biologic, non-JAKi systemic therapies

(comparator medications) approved for the treatment of AD at the time of registry enrollment. Where feasible, a cohort of European [EUR]-residing adolescents with moderate to severe AD will also be evaluated.

Objectives:

The primary objectives of the study are to (1) compare changes from baseline in height standard deviation score (SDS) and weight SDS, (2) compare somatic maturity timing measured by age at peak height velocity, (3) compare changes from baseline in pubertal progression as measured by Tanner stage, and (4) compare the incidence rates of bone fractures in adolescents with moderate to severe AD treated with upadacitinib and those treated with biologic or other non-biologic, non-JAKi systemic therapies (comparator medications) for AD.

Secondary objectives of the study are to describe changes from baseline in standing height, height percentiles, height velocity, height velocity SDS, weight, weight percentiles, body mass index (BMI), BMI percentiles, and BMI SDS, as well as the frequency of delayed puberty in adolescents with moderate to severe AD treated with upadacitinib and those treated with biologic or other non-biologic, non-JAKi systemic therapies (comparator medications) for AD.

Study Design:

This will be an observational, prospective cohort study of adolescents who receive upadacitinib or biologic or other non-biologic, non-JAKi systemic therapies approved for the treatment of moderate to severe AD at the time of registry enrollment.

Population:

The study population will be drawn from patients enrolled in the CorEvitas Adolescent AD Registry. The clinical patient registry will enroll younger adolescents (12-15 years old) with moderate to severe AD in the United States (US), Canada, and Europe. The primary study analyses will include cohorts of adolescents newly prescribed upadacitinib

for the treatment of moderate to severe AD in routine clinical care in North American sites (US and Canada), with secondary analyses including cohorts from Europe (e.g., Austria, Belgium, Portugal, Turkey, and Norway). The comparator cohort will include patients with moderate to severe AD newly prescribed biologic or other non-biologic, non-JAKi systemic therapies approved for the treatment of AD at the time of registry enrollment.

Variables:

Upadacitinib is the exposure of interest. The exposure variable for the drug comparator cohort will be biologic and other non-biologic, non-JAKi systemic therapies approved in the US, Canada, or Europe for the treatment of moderate to severe AD, including the biologic dupilumab as well as other non-biologic, non-JAKi systemic therapies approved for the treatment of moderate to severe AD at the time of registry enrollment. Exposure is reported by the physician at enrollment into the registry, and changes to exposure are reported by the physician at follow-up visits.

Primary study outcomes include changes from baseline in height SDS and weight SDS from the cohort entry date to the end of follow-up. Additional outcomes include somatic maturity timing measured by age at peak height velocity (PHV), changes in pubertal progression as measured by Tanner stage, and the incidence of bone fractures.

Other variables that are routinely collected as part of the CorEvitas Adolescent AD Registry will be included in this study, including demographics, race, ethnicity, disease activity, past and present medication use, comorbidities, lifestyle factors, and other factors that may affect growth (e.g., parental height).

Data Source:

Primary and secondary endpoints of interest for the study will be explicitly and prospectively collected using the CorEvitas Registry Questionnaires. Data collection will continue for as long as the patient remains enrolled in the registry. Adolescent growth and

maturation will be assessed at enrollment and at each registry follow-up visit, in addition to active assessments for the occurrence of adverse events and other adverse events of special interest, which will be assessed per the standard registry model. Patients' height and weight measures performed in the 5-year period prior to registry enrollment will be obtained from their pediatricians' records. Adolescents will be followed from the cohort entry date to the earliest occurrence of turning 18 years old, initiating another JAKi, withdrawing or exiting from the registry, or reaching the end of study period.

As part of the standard registry model, any physician-reported adverse events will be captured using the Provider Follow-up, Exit and Targeted Event Questionnaires (as applicable). As bone fractures are safety events of interest for purposes of this PASS, additional details pertaining to fracture events will be captured using a dedicated Bone Fracture Targeted Adverse Event Questionnaire (TAEQ). These data will be used to support analyses of bone fracture outcomes. The Fracture TAEQ will be auto generated by CorEvitas' electronic data capture (EDC), prompting completion by the site whenever a fracture is reported via the Provider Follow-up or Exit Questionnaires. Sites are required, per the registry protocol, to submit source documentation as appropriate to support medical review with validation, and further characterization of the nature of the fracture event.

Additional variables required for the planned analyses are captured using CorEvitas registry Provider and Subject Enrollment and Follow-up, and Exit Questionnaires.

Study Size:

All adolescents enrolled in the CorEvitas Adolescent AD Registry who initiate upadacitinib or a comparator medication approved for treatment of AD during the study enrolment period and meet study eligibility criteria will be included in the analysis. Based on the available data, it is expected that the final report will include at least 500 adolescents (250 patients in each exposure cohort) from North America and 200 (100 patients in each exposure cohort) from Europe.

Data Analysis:

For each exposure cohort for the primary analyses (i.e., NA-residing adolescents), patient characteristics at baseline, including demographics, clinical and disease characteristics, treatment history, and patient reported outcomes (PROs) will be described. Descriptive summary statistics will be provided for each study outcome. Changes for growth-related measures from baseline to end of follow-up will be described overall for all adolescents and by exposure cohort, including changes in height SDS and weight SDS. Age at peak height velocity (PHV) will be described by exposure cohort. The incidence of bone fractures during the follow-up period will be described by exposure cohort. Propensity score methods will be used to account for differences between exposure cohorts at baseline. Changes in height SDS, changes in weight SDS, age at PHV, age at Tanner stage progression, and incidence of bone fractures will be compared between the two propensity score trimmed exposure cohorts from North America. As secondary analyses, the proposed analyses will be repeated among the European population including descriptive statistics and comparative analyses where feasible.

Milestones:

AbbVie will initiate the study upon endorsement of the study protocol by the EMA and following IRB approval of the registry protocol. A final study report is anticipated to be submitted to the EMA by the end of 2033.

Investigators:

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