In utero or early in life exposure to antibiotics and the risk of childhood atopic dermatitis, a population-based cohort study

Running head: Atopic dermatitis: Antibiotics from mom to child.

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Conflicts of interest: DJM is or recently has been a consultant for Pfizer, Leo, and Sanofi with respect to studies of atopic dermatitis and served on an advisory board for the National Eczema Association. ZCCF has received research grants from Lilly, LEO Pharma, Regeneron, Sanofi, Tioga, and Vanda for work related to atopic dermatitis and from Menlo Therapeutics and Galderma for work related to prurigo nodularis. She has also served as consultant for the Asthma and Allergy Foundation of America, National Eczema Association, AbbVie, Incyte Corporation, and Pfizer; and received honoraria for CME work in Atopic Dermatitis sponsored by education grants from Regeneron/Sanofi and Pfizer and from Beirsdorf for work related to skin cancer and sun protection. The other authors do not report potential conflicts of interest with respect to the materials in this manuscript. NM, DDP, OH, DBS, SML, IP, and KB report no conflicts of interest.

Data availability: IQVIA Medical Research Data (IMRD) dataset, which incorporates data from The Health Information Network (THIN), a Cegedim Database is available for purchase from IQVIA.

Ethics statement: The study was approved by IMRD, the Scientific Review Committee (SRC) for UK Ethics as protocol number 22SRC042, and the University of Pennsylvania Institutional Review Board (IRB).

What is already known about this topic?

- Atopic dermatitis is thought to be associated with changes to a child's microbiota. Previous studies have indicated that the use of antimicrobials by the mother during pregnancy and by the child increase the risk of the child developing atopic dermatitis.

What does this study add?

- Using a large population-based cohort study we demonstrate that both in utero and first 90 days of life exposure to antibiotics increase the risk of atopic dermatitis in the child. This risk is highest for penicillin exposure and the relative risk is higher for child whose mothers did not have atopic dermatitis.

Abstract

Background: Atopic dermatitis (AD) is a common inflammatory disease of the skin that begins early in life and can be lifelong. The purpose of our study was to evaluate whether fetal exposure and/or early life exposure of a child to antibiotics increases the risk of early onset AD.

Objective: We hypothesize that antibiotic exposure *in utero* or early in life (e.g., first 90 days) increases the likelihood that children develop AD.

Methods: Utilizing a large prospectively collected electronic medical records database, we studied the association of antibiotic exposure received *in utero* or very early in life and the relative risk of onset of AD in a population-based cohort study. Associations were estimated using proportional hazards models as hazard ratios (HR) with 95% confidence intervals (CI).

Results: The risk of AD in childhood was increased after *in utero* or early life antibiotic exposure. For any *in utero* AB exposure the HR was 1.38 (1.36,1.39). However, penicillin demonstrated the strongest association with AD for both *in utero* exposure, 1.43 (1.41,1.44), and for childhood exposure, 1.81(1.79,1.82). HRs were higher in children born to mothers without AD than those with AD pointing to effect modification by maternal AD status.

Conclusion: Children born to mothers exposed to antibiotics while *in utero* had, depending on the mother's history of AD, approximately a 20 to 40% increased risk of developing AD. Depending on the antibiotic, children who received antibiotics early-in-life had a 40 to 80% increased risk of developing AD. Our study, supports and refines the association between incident AD and antibiotic administration. It also adds population-based support to therapeutic attempts to treat AD by modifying skin microbiome.

Introduction

Atopic dermatitis (AD) or atopic eczema is one of the most common inflammatory diseases of the skin and one of the most common chronic allergic/atopic diseases.[1] For many, it occurs early in life and it can be a lifelong disease.[2] AD may co-occur with other allergic illnesses (OAI) like asthma, seasonal allergies, and food allergies and often occurs prior to their onset. [2-4] While full elucidation of the pathogenesis of AD remains incomplete, it is thought to involve a complex interplay between genetics, skin barrier dysfunction, immune dysregulation, alterations in the skin microbiome, and exposure to environmental factors.[5-7] Many investigators have shown that AD is strongly associated with T-cell dysregulation and has therefore been classified as an autoimmune illness.[8-11] Patients with AD have altered skin microbiota as compared to those without AD and changes in the skin microbiota are associated with changes in AD disease severity.[12-17]

Exposure to antimicrobials can induce changes to the gut and skin microbiota.[15,18] Antibiotics in particular are among the most commonly used drugs in infants and children and exposure to antibiotics has been associated with an increased risk of developing AD in this population.[19] However, very few studies have evaluated antimicrobial exposures during pregnancy (i.e., *in utero*) and few within the first year of a child's life and the potential association with AD.[20-28] While these studies have shown an association between antibiotic exposure and subsequent development of AD, the internal and external validity of many of these studies has often been hampered by recall bias, as most have relied on the mother's recollection of the timing of the child's antibiotic exposure, antibiotic exposure during pregnancy, as well as the onset of her child's AD. [20,24,26-31]

New therapeutics for AD have primarily focused on immune mechanisms, however, social and environmental factors have been associated with AD.[32,33] Exposure to "environmental factors" could begin *in utero* and/or early in the child's life. The neonatal *in utero* environment may be directly affected by the administration of antibiotics, it could have metabolic effects to the mother that are transmitted across the placenta to the neonate, and/or change in the mother's microbiome.[34-36] With respect to direct changes of the skin microbiome that might induce AD, recent early phase human studies have

been based on changing the microbiome of an individual with active AD in order to treat AD in the short term and manage in the long term AD.[37]

The purpose of our study was to evaluate whether fetal exposure and early life exposure of antibiotics increases a child's risk of early onset AD. We hypothesize that a child who is born to a pregnant female who received antibiotics during pregnancy is at greater risk of developing AD compared to children born to mothers who did not receive antibiotics and that children exposed to antibiotics are more likely to develop AD compared to children without antibiotic exposure. For this study, we utilized a United Kingdom (UK) patient records database merging primary care health records of mothers and their babies focusing on *in utero* and early in life antibiotic exposures and a child's subsequent diagnosis of AD.

Methods

Population: In the United Kingdom (UK) there are several databases that hold anonymized patient electronic health records. For this study, we used the IQVIA Medical Research Data (IMRD) dataset, which incorporates data from The Health Information Network (THIN), a Cegedim Database. Any reference to THIN is intended to be descriptive of the licensed IMRD dataset. This database includes anonymized longitudinal general practice (GP) data from a patients' clinical and prescribing records. Medications prescribed utilizing the electronic health record are generally provided via a program from the NHS at minimal cost to the patient and during pregnancies these medications are provided for free. IMRD includes data from 832 practices, across the UK, which cover approximately10% of the UK population, and is believed to be representative of the full UK population.[38,39]

Definition of study population: Diagnoses and symptoms are recorded by practice staff using Read codes, a numerical classification system developed to record health-care related diagnosis and symptoms.[38-40] Data collection for our study was from 2004 to 2021. Our study focused on children that

were registered to their GP within 60 days of their reported delivery date and with at least two visits to the GP. To match mother and child, all mother-child pairs had to use the same GP and had to reside in the same household. This method is consistent with prior published work.[39,41] Approximately, one million babies were matched to their mothers using this method. This was a cohort study, the child was the primary unit of analysis, and the mother's history of antibiotic exposure during pregnancy or the child's first history of exposure to antibiotics as the primary exposure.

Exposure and outcome definition: Antibiotic exposure was based on prescriptions entered into the electronic health record. Antibiotics were placed in common categories with the four most common groups being penicillin, macrolide, sulfa (e.g., sulfonamide and combinations), and cephalosporins. The primary outcome of interest was incident AD in the child. The method for ascertaining the diagnosis of AD has been previously validated in this database.[42]

Analysis: Descriptive statistics were used to summarize categorical and continuous variables using proportions (percentages, %) and means (standard deviation, SD), or medians (interquartile range. Statistical models were used to evaluate the association of maternal *in utero* antibiotic use or the association of childhood antibiotic use on the development of AD in the child. As appropriate, additional variables included in the analyses were the mother's history of illnesses such as AD (well known to be associated with risk of childhood AD), and other allergic illnesses OAI (i.e. seasonal allergies, asthma and food allergy); children's history of OAI (current or later document), Townsend's score (index of socioeconomic deprivation reported as quintiles and dichotomized by the two quintiles of greatest social deprivation); ethnicity; and the child's assigned sex at birth. All babies were followed from the date of delivery until they transferred out of the GP's practice, died, developed the outcome of interest (AD) or until the end of database reporting period (administrative censoring). All evaluations were based on the presence or absence of the evaluated exposure/covariate. Cox proportional hazards models were used to evaluate the association between mother's risk factors with the time of onset of AD in the child. Effect

estimates are reported as hazard ratios (HR) with 95% confidence intervals (CI). Because *a priori* the mother's history of AD was assumed to be strongly associated with a child's risk of AD, this exposure was also viewed as an effect modifier, therefore HR are reported for children based on their maternal history of AD. With respect to antibiotic exposure in the child, the first exposure time varied. In addition, antibiotic exposure had to occur prior to the child's diagnosis of AD. Our analyses allowed for clustering within mother, since a mother may have had more than one child. In secondary analyses, we created exposure matched sibling cohorts in which one sibling was antibiotic exposed and one was not exposed. If more than one sibling was available for matching, then one sibling was randomly chosen. The sibling pairs had the same mother, the same GP, and grew up in the same location. Separate cohorts were created for each type of exposure such as *in utero* penicillin, penicillin in childhood, etc. These secondary studies allowed us to control for environmental and genetic factors that could be associated with AD. These results are reported in a supplement.

Analyses were conducted using Stata MP version 18. This study was reported in accordance with STROBE guidelines for reporting of observational studies using routinely collected data. The study was approved by IMRD, the Scientific Review Committee (SRC) for UK Ethics as protocol number 22SRC042, and the University of Pennsylvania Institutional Review Board (IRB).

Results

Between 2004 and 2021, 1,023,140 mother-child pairs were identified. Children were followed on average for 10.2 (sd:7.9) years resulting in more than 10 million person-years of follow-up. The average age of diagnosis of AD was 3.2 (sd:4.6) years. Characteristics of the children are displayed in Table 1 and Supplement Table 1. Supplement Table 1 describes characteristics based on antibiotic exposure status. As expected, a history of AD in the mother was highly associated with AD in childhood (HR: 1.71 (95%CI:1.96,1.72)) as was a diagnosis of asthma, seasonal allergies, and food allergies (Table 2). However, risks associated with ethnicity, gender assigned at birth, and Townsend index were

much less. In general, during follow up, children with AD were more likely to receive an antibiotic (88.21% (88.46, 88.33) than those without AD 67.34% (67.45,67. 56), respectively).

The risks of AD in children exposed to antibiotic *in utero* are summarized in Table 2. The HR (95% CI) of AD in childhood was increased after *in utero* antibiotic exposure (HR:1.38 95% CI:(1.36,1.39)). The effect of *in utero* antibiotic exposure did not depend on the trimester administered (Table 2). Overall, the association between any antibiotic exposure and a child's risk of AD was greater in children born to mothers who did not have a history of AD (Tables 1 and 2). *In utero* exposure to penicillin was associated with the largest hazard ratio,1.43 (1.41,1.44). This effect was not significantly altered after adjusting for maternal AD and OAI, maternal exposure to antibiotics, sex of the child assigned at birth, Townsend's index, and ethnicity. Maternal history of AD is an effect modifier with respect to the risk of all antibiotics (p-value < 0.00001 in all cases) (Table 2).

Table 3 summarizes the risk of AD after exposure to antibiotics in childhood. As noted above, children exposed to penicillin were more likely to develop AD than children not exposed to antibiotics (1.81(1.79,1.82)). This association changed minimally in the adjusted models (Table 3). As noted above these effects were also modified by the mother's AD status. For example, for penicillin, the effect was greater in children from mothers who did not have AD (1.81(1.79,1.82)) versus mother with AD (1.52(1.50,1.55)). Table 4 summarizes the association between early (within the first 90 days of life) antibiotic and development of AD. For example, children with early penicillin exposure had a 70% increased risk of developing AD compared to children not exposed early to penicillin (1.70(1.67,1.73)). This effect was greater in children born to mothers with no history of AD (1.71(1.68,1.75)) than children born to mothers with AD (1.45(1.40,1.50)). Sensitivity analysis matching siblings exposed to antibiotics and not exposed to antibiotics born to the same mothers and living in the same household resulted in similar findings. These results are available in the supplement (Supplement Table 2).

Discussion

In our study, children born to mothers exposed to antibiotics while *in utero* had approximately a 20 to 40% increased risk of developing AD. Interestingly, we observed that the hazard ratio of a child developing AD following first exposure to antibiotics was greater in children born to mothers who did not have a personal history of AD and that the risk was higher among those exposed to penicillin. Using models that allowed the first exposure to antibiotics to vary with time, children who received antibiotics had a 40 to 80% increased risk of developing AD by age 3. This risk was not statistically different after adjustment and not confounded by the mother's history of AD and OAIs nor mother's history of having received antibiotics during her pregnancy. Furthermore, the risk was not significantly altered by the child having a future tendency towards having allergic illnesses as represented by OAI. We also observed that the effect of antibiotic exposure was larger during the first 90 days of life. In addition, similar results to our primary analyses were found when we controlled for unmeasured common family exposures like environmental exposures by matching children who did or did not have antibiotic exposure but were born to the same mother and lived in the same house.

Previous studies have investigated *in utero* and childhood exposure to antibiotics and the onset of AD. These studies include a retrospective cohort survey study that relied on subject recall using data from the *Growing Up Today Study*, a cohort of the Nurses' Health study II.[28] This study relied on questionnaires answered retrospectively by mothers and evaluated antibiotic exposure during pregnancy as well as during the first 18 months of life.[28] Physician diagnosed AD in the child as reported by the mother was increased after antibiotic exposure (Odds Ratio (OR)=1.44 (1.21,1.72)) and early in life (OR:1.37 (1.19,1.57)).[28] The authors noted that their study could have been limited by recall bias and AD self-reporting.[28] A separate study of 492 mother-baby pairs, intrapartum antibiotics for more than 24 hours increased the risk of AD by age 2 (Relative Risk (RR)=1.99 (1.13,3.49)) but if administered for less than 24 hours during a vaginal delivery it did not.[21] A prospective birth cohort of 976 mother baby pairs in China also found an increased risk of eczema (OR=3.59 (1.19,10.85)) in babies exposed to *in utero* antibiotics.[27] A study of 1,080 children from a European birth cohort that

used questionnaires to collect information on antibiotic use reported an increased risk of AD after prenatal antibiotic exposure (OR=1.55(1.08,2.24)) and an increased risk of AD after exposure of antibiotics in the first year of life (OR=2.57(1.91,3.44)).[24] It is important to note that for most of these studies, recall and ascertainment bias could be problematic as they relied primary of questionnaires administered to the mother later in life. Our findings help support and expand our current understanding of this association and suggest that antibiotic exposure is a potential risk factor for childhood onset AD.

We also observed that use of certain antibiotic classes confers an increased risk of early onset AD. Similar findings have been observed in other studies although the risk varies by type of antibiotics. A prospective study of 370 children initially without AD demonstrated an increased risk of AD in those exposed to macrolide (RR=2.15(1.18,3.91)) and cephalosporin (RR=1.93(1.07,3.49)) antibiotics given in the first year of life.[29] Another study utilizing questionnaires also established an increased risk of eczema in a birth cohort of over 62,000 mother baby pairs after early prenatal antibiotics (OR=1.45(1.19,1.76)), however, exposure in the last trimester was not associated with eczema.[30] The largest previous study, with similar design to ours, also used health records and merged the Swedish Prescribed Drug Register, National Patient Register, and the Swedish Medical Birth Register.[22] About 21.2% of children were exposed to antibiotics *in utero* and 23.8% were exposed in the first year of life.[22] There was an increased risk of AD in children exposed *in utero* (HR=1.10 (1.09,1.12)) and in the first year of life (HR=1.52 (1.50,1.55)). Using a sibling matched analysis, the *in utero* effect became null but the early exposure effect was maintained.[22] In contrast, a prospective UK based study attempted to better control potential confounders and noted that prenatal antibiotic administration was not associated with childhood AD but antibiotic exposure during a child's first year of life was associated with childhood AD.[20] However, the methods utilized for this study including the selection of confounders appears to be problematic.[43] In addition, a study of 2,909 mother baby pairs in Eastern China that used questionnaires and hospital records noted that intra-partum use of antibiotics to treat GBS was associated with an increased risk (OR=2.54 (1.80,3.61)) of AD by age 2.[26] Other investigations have

demonstrated that intrapartum antibiotic prophylaxis for GBS does have an effect on the infant's microbiota.[25]

Our study has several strengths including its large sample size and its rich data source collected prospectively by healthcare providers, from birth to up to on average 10 years of follow up. This allowed us to uniquely analyze the effect of history of maternal atopic illnesses on the association of antibiotic exposure. We also used time varying models to capture variation in antibiotic exposure over time. The limitations of our study include potential errors in linking mother and child. However, the method that we used to link pregnant women to their newborn has been validated in a similar database.[39,41,44] It is possible that protopathic bias (i.e., the antibiotic was prescribed for an early manifestation of AD) was associated with our findings. We were careful to assure that antibiotic exposures occurred prior to the child's diagnosis of AD (e.g., *in utero* and first 90 days of life). In addition, the effect of antibiotic administration early in life was mitigated in children with the highest anticipated risk of early onset AD (i.e., those born to mothers with AD, seasonal allergies, food allergies, and/or asthma). Information bias could influence the recording of medical information or the willingness of a parent to bring their child to the GP for examination and treatment. Furthermore, mothers with AD could be more likely to seek healthcare. While this is might be possible, in our cohort, the mothers and children used the same GP (i.e., the medical practice already being used by the mother), all pregnant women and children received free healthcare and prescriptions in the UK. The effect of antibiotics on childhood AD was greater in children whose mothers did not have AD, thereby, decreasing the likelihood that maternal antibiotic use was confounded by other variables. In our secondary analysis, which focused on babies born to the same mother, the effects of antibiotic were like our primary analyses. Medical information evaluated in this study were from the GP record so it is possible for that antibiotics administered only in hospital may not have been recorded in the GP record and therefore not available for evaluation.

In conclusion, this longitudinal cohort study that utilized medical records, supports, and more importantly refines the association between incident AD and antibiotic administration during pregnancy as well as in the early life period. It is not known why exposure to antibiotics *in utero* and early in life

might be associated with AD, but it has been hypothesized that antibiotics may play a role in immune dysregulation due to an impaired development of a robust gut microbiome.[15,18,45] While this is not a new practice guideline, healthcare providers should carefully consider the need for antibiotics before using them.[46,47] While our findings are consistent with this message, causation has not been established and other alternative methods for altering the human microbiome while treating AD are still being developed. [37,48,49]

References

1 Hay RJ, Johns NE, Williams HC *et al.* The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. *Journal of Investigative Dermatology* 2014; **134**: 1527-34.

2 Mortz CG, Andersen KE, Dellgren C *et al.* Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. *Allergy* 2015; **70**: 836-45.

3 Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol* 2017; **139**: 1723-34.

4 Dharmage SC, Lowe AJ, Matheson MC *et al.* Atopic dermatitis and the atopic march revisited. *Allergy* 2014; **69**: 17-27.

5 Eyerich K, Eyerich S, Biedermann T. The Multi-Modal Immune Pathogenesis of Atopic Eczema. *Trends Immunol* 2015; **36**: 788-801.

6 Narla S, Silverberg JI. The Role of Environmental Exposures in Atopic Dermatitis. *Curr Allergy Asthma Rep* 2020; **20**: 74.

7 Gabryszewski SJ, Dudley J, Shu D *et al.* Patterns in the Development of Pediatric Allergy. *Pediatrics* 2023; **152**.

8 Leung DY, Bieber T. Atopic dermatitis. [Review] [100 refs]. *Lancet* 2003; **361**: 151-60.

9 Agrawal R, Wisniewski JA, Woodfolk JA. The role of regulatory T cells in atopic dermatitis. *Curr Probl Dermatol* 2011; **41**: 112-24.

10 Harris VR, Cooper AJ. Atopic dermatitis: the new frontier. *Med J Aust* 2017; **207**: 351-6.

11 Renert-Yuval Y, Guttman-Yassky E. New treatments for atopic dermatitis targeting beyond IL-4/IL-13 cytokines. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology* 2020; **124**: 28-35.

12 Kong HH, Oh J, Deming C *et al.* Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis. *Genome Research* 2012; **22**: 850-9.

13 Paller AS, Kong HH, Seed P *et al.* The microbiome in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019; **143**: 26-35.

14 Byrd AL, Deming C, Cassidy SKB *et al.* Staphylococcus aureus and Staphylococcus epidermidis strain diversity underlying pediatric atopic dermatitis. *Sci Transl Med* 2017; **9**: 1-12.

15 Jo JH, Harkins CP, Schwardt NH *et al.* Alterations of human skin microbiome and expansion of antimicrobial resistance after systemic antibiotics. *Sci Transl Med* 2021; **13**: 1-13, eabd8077.

16 Beck LA, Bieber T, Weidinger S *et al.* Tralokinumab treatment improves the skin microbiota by increasing the microbial diversity in adults with moderate-to-severe atopic dermatitis: Analysis of microbial diversity in ECZTRA 1, a randomized controlled trial. *Journal of the American Academy of Dermatology* 2023; **88**: 816-23.

17 Koh LF, Ong RY, Common JE. Skin microbiome of atopic dermatitis. *Allergol Int* 2022; **71**: 31-9.
18 Anthony WE, Wang B, Sukhum KV *et al.* Acute and persistent effects of commonly used antibiotics on the gut microbiome and resistome in healthy adults. *Cell Rep* 2022; **39**: 110649.
19 Duong QA, Pittet LF, Curtis N, Zimmermann P. Antibiotic exposure and adverse long-term health outcomes in children: A systematic review and meta-analysis. *Journal of Infection* 2022; **85**: 213-300.
20 El-Heis S, Crozier SR, Harvey NC *et al.* Early life exposure to antibiotics and laxatives in relation to infantile atopic eczema. *Pediatr Allergy Immunol* 2023; **34**: e13964.
21 Wohl DL, Curry WJ, Mauger D *et al.* Intrapartum Antibiotics and Childhood Atopic Dermatitis. *The Journal of the American Board of Family Medicine* 2015; **28**: 82-9.
22 Mubanga M, Lundholm C, D'Onofrio BM *et al.* Association of Early Life Exposure to Antibiotics With Risk of Atopic Dermatitis in Sweden. *JAMA Netw Open* 2021; **4**: e215245.
23 Schoch JJ, Satcher KG, Garvan CW *et al.* Association between early life antibiotic exposure and development of early childhood atopic dermatitis. *JAAD Int* 2023; **10**: 68-74.
24 Metzler S, Frei R, Schmaußer-Hechfellner E *et al.* Association between antibiotic treatment during pregnancy and infancy and the development of allergic diseases. *Pediatr Allergy Immunol* 2019; **30**: 423-33.
25 Prescott S, Dreisbach C, Baumgartel K *et al.* Impact of Intrapartum Antibiotic Prophylaxis on Offspring Microbiota. *Front Pediatr* 2021; **9**: 754013.
26 Hong Z, Jing R, Hui L *et al.* A cohort study of intrapartum group B streptococcus prophylaxis on atopic dermatitis in 2-year-old children. *BMC Pediatr* 2022; **22**: 693.
27 Gao X, Yan Y, Zeng G *et al.* Influence of prenatal and early-life exposures on food allergy and eczema in infancy: a birth cohort study. *BMC Pediatr* 2019; **19**: 239.
28 Vance TM, Li T, Cho E *et al.* Prenatal antibiotic use and subsequent risk of atopic eczema. *British Journal of Dermatology* 2022; **188**: 561-3.
29 Schmitt J, Schmitt NM, Kirch W, Meurer M. Early exposure to antibiotics and infections and the incidence of atopic eczema: a population-based cohort study. *Pediatr Allergy Immunol* 2010; **21**: 292-300.
30 Timm S, Schlünssen V, Olsen J, Ramlau-Hansen CH. Prenatal antibiotics and atopic dermatitis among 18-month-old children in the Danish National Birth Cohort. *Clin Exp Allergy* 2017; **47**: 929-36.
31 Bittinger K, Zhao C, Li Y *et al.* Bacterial colonization reprograms the neonatal gut metabolome. *Nat Microbiol* 2020; **5**: 838-47.
32 Stefanovic N, Flohr C, Irvine AD. The exposome in atopic dermatitis. *Allergy* 2020; **75**: 63-74.
33 Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. *Lancet* 2020; **396**: 345-60.
34 Gonçalves BP, Procter SR, Paul P *et al.* Group B streptococcus infection during pregnancy and infancy: estimates of regional and global burden. *Lancet Glob Health* 2022; **10**: e807-e19.
35 Campbell JR, Hillier SL, Krohn MA *et al.* Group B streptococcal colonization and serotype-specific immunity in pregnant women at delivery. *Obstet Gynecol* 2000; **96**: 498-503.
36 ACOG. Prevention of Group B Streptococcal Early-Onset Disease in Newborns: ACOG Committee Opinion, Number 797. *Obstet Gynecol* 2020; **135**: e51-e72.
37 Nakatsuji T, Hata TR, Tong Y *et al.* Development of a human skin commensal microbe for bacteriotherapy of atopic dermatitis and use in a phase 1 randomized clinical trial. *Nat Med* 2021; **27**: 700-9.
38 Denburg MR, Haynes K, Shults J *et al.* Validation of The Health Improvement Network (THIN) database for epidemiologic studies of chronic kidney disease. *Pharmacoepidemiol Drug Saf* 2011; **20**: 1138-49.
39 Davé S, Petersen I. Creating medical and drug code lists to identify cases in primary care databases. *Pharmacoepidemiology and Drug Safety* 2009; **18**: 704-7.

40 Lo Re V, 3rd, Haynes K, Forde KA *et al.* Validity of The Health Improvement Network (THIN) for epidemiologic studies of hepatitis C virus infection. *Pharmacoepidemiol Drug Saf* 2009; **18**: 807-14.
41 Minassian C, Williams R, Meeraus WH *et al.* Methods to generate and validate a Pregnancy Register in the UK Clinical Practice Research Datalink primary care database. *Pharmacoepidemiol Drug Saf* 2019; **28**: 923-33.
42 Abuabara K, Magyari AM, Hoffstad O *et al.* Development and Validation of an Algorithm to Accurately Identify Atopic Eczema Patients in Primary Care Electronic Health Records from the UK. *J Invest Dermatol* 2017; **137**: 1655-62.
43 Fuxench ZC, Mitra N, Margolis DJ. Comment on El-Heis et al. *Pediatric Allergy and Immunology* 2023; **34**: e13985.
44 Petersen I, Sammon CJ, McCrea RL *et al.* Risks associated with antipsychotic treatment in pregnancy: Comparative cohort studies based on electronic health records. *Schizophr Res* 2016; **176**: 349-56.
45 Gomez de Agüero M, Ganal-Vonarburg SC, Fuhrer T *et al.* The maternal microbiota drives early postnatal innate immune development. *Science (New York, N.Y.)* 2016; **351**: 1296-302.
46 Fleming-Dutra KE, Hersh AL, Shapiro DJ *et al.* Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011. *Jama* 2016; **315**: 1864-73.
47 National Academies of Sciences E, Medicine. *Combating Antimicrobial Resistance and Protecting the Miracle of Modern Medicine*. Washington, DC: The National Academies Press. 2022.
48 Nakatsuji T, Gallo RL, Shafiq F *et al.* Use of Autologous Bacteriotherapy to Treat Staphylococcus aureus in Patients With Atopic Dermatitis: A Randomized Double-blind Clinical Trial. *JAMA Dermatology* 2021; **157**: 978-82.
49 Ito Y, Amagai M. Controlling skin microbiome as a new bacteriotherapy for inflammatory skin diseases. *Inflammation and Regeneration* 2022; **42**: 26.

Table 1: Characteristics and demographics of the children in the study. Characteristics are also displayed based on the final AD[a] outcome. Characteristics based on antibiotic exposure status are available in supplement Table 1. Frequencies are area based on the presence or absence of the covariate and presented as percentage and 95% CI except for age, which is presented as mean and sd. *Birth to end of study period (e.g., age of child at the end of the study period)

	Full cohort	Child without AD	Child with AD
Average follow up* (mean, sd)	10.2(sd:7.9)	9.7(7.9)	11.6(7.6)
Ethnicity white (%)	71.22(71.13,71.31)	71.87(71.77,71.97)	69.30(69.12,69.48)
Townsend index (≥ 4)	29.02(28.93,29.11)	29.67(29.57,29.77)	27.10(26.93,27.27)
Child with AD(%)	25.32(25.24,25.40)	0.00(0.00,0.00)	100.00(100.00,100.00)
Child with food allergy(%)	0.90(0.89,0.92)	0.45(0.44,0.47)	2.23(2.18,2.29)
Child with asthma(%)	12.98(12.92,13.05)	10.31(10.24,10.37)	20.88(20.73,21.04)
Child with seasonal allergies(%)	7.96(7.91,8.01)	5.81(5.76,5.87)	14.29(14.16,14.43)
Mother with AD(%)	14.96 (14.90,15.03)	12.54(12.47,12.62)	22.10(21.94,22.26)
Mothers receiving any antibiotic during pregnancy(%)	18.11(18.04,18.19)	17.08(17.00,17.17)	21.15(20.99,21.30)
Children receiving any antibiotic during observation(%)	72.74(72.65,72.82)	67.45(67.34,67.56)	88.33(88.21,88.46)
Penicillin(%)	68.61(68.52,68.70)	63.17(63.07,63.28)	84.64(84.50,84.78)
First 90 days(%)	3.03(3.00,3.07)	2.56(2.53,2.60)	4.42(4.34,4.50)
Cephalosporin(%)	9.73(9.67,9.79)	8.20(8.14,8.26)	14.24(14.10,14.37)
First 90 days(%)	0.14(0.13,0.14)	0.11(0.10,0.12)	0.21(0.20,0.23)
Sulfa (%)	13.22(13.16,13.29)	11.61(11.54,11.68)	17.99(17.84,18.13)
First 90 days(%)	0.29(0.28,0.30)	0.26(0.25,0.27)	0.37(0.34,0.39)
Macrolide(%)	25.33(25.25,25.41)	21.51(21.41,21.60)	36.61(36.42,36.79)
First 90 days(%)	0.42(0.41,0.44)	0.35(0.34,0.36)	0.65(0.61,0.68)
Penicillin mother(%)			
First trimester (%)	2.08(2.05,2.11)	2.03(2.00,2.07)	2.22(2.17,2.28)
Second trimester (%)	3.03(2.99,3.06)	2.89(2.86,2.93)	3.42(3.35,3.49)
Second or third trimester (%)	10.76(10.70,10.82)	10.01(9.94,10.08)	12.96(12.83,13.09)
Last trimester(%)	7.73(7.68,7.78)	7.12(7.06,7.17)	9.54(9.43,9.65)
Sulfa mother(%)			
First trimester (%)	0.22(0.21,0.23)	0.23(0.22,0.24)	0.20(0.19,0.22)
Second trimester (%)	0.20(0.19,0.21)	0.20(0.19,0.21)	0.21(0.19,0.23)
Second or third trimester (%)	0.74(0.73,0.76)	0.71(0.70,0.73)	0.82(0.79,0.86)
Third trimester (%)	0.54(0.53,0.55)	0.52(0.50,0.53)	0.61(0.58,0.64)
Cephalosporin mother(%)			
First trimester (%)	1.31(1.29,1.33)	1.29(1.26,1.31)	1.38(1.34,1.43)
Second trimester (%)	1.24(1.22,1.26)	1.18(1.16,1.20)	1.42(1.38,1.47)
Second or third trimester (%)	3.61(3.57,3.64)	3.37(3.33,3.41)	4.30(4.22,4.38)
Third trimester (%)	2.36(2.33,2.39)	2.19(2.16,2.22)	2.88(2.82,2.94)
Macrolide mother(%)			
First trimester (%)	0.33(0.32,0.34)	0.33(0.32,0.34)	0.35(0.33,0.37)
Second trimester (%)	0.41(0.39,0.42)	0.39(0.38,0.40)	0.46(0.43,0.48)
Second or third trimester (%)	1.40(1.38,1.42)	1.29(1.27,1.32)	1.73(1.68,1.78)
Third trimester (%)	0.98(1.01,0.99)	0.88(0.92,0.90)	1.23(1.32,1.27)

[a]AD=atopic dermatitis; [b]sd=standard deviation; [c](%)=percentage; [d]top 40% most socially deprived

Table 2: The association of the presence or absence of exposures and factors in Mothers on their children with respect to the onset of childhood atopic dermatitis. Effect estimates are expressed as hazard ratios with 95% confidence intervals. AD- atopic dermatitis

	Full cohort	Moms without AD	Moms with AD
Mother with AD	1.71(1.69,1.72)		100(100,100)
White ethnicity	0.93(0.92,0.94)	0.93(0.93,0.94)	0.98(0.97,1.00)
Townsend index	0.94(0.93,0.95)	0.93(0.92,0.94)	0.94(0.93,0.96)
Seasonal allergies	1.45(1.44,1.47)	1.40(1.38,1.42)	1.25(1.23,1.27)
Asthma	1.18(1.17,1.19)	1.11(1.10,1.13)	1.09(1.07,1.11)
Food allergy	1.59(1.50,1.69)	1.38(1.27,1.49)	1.47(1.35,1.60)
Penicillin	1.43(1.41,1.44)	1.42(1.40,1.44)	1.20(1.18,1.22)
First trimester	1.31(1.28,1.35)	1.35(1.30,1.39)	1.05(1.00,1.11)
Second trimester	1.43(1.40,1.46)	1.45(1.41,1.48)	1.18(1.13,1.23)
Second or third trimester	1.43(1.41,1.45)	1.42(1.40,1.44)	1.22(1.19,1.24)
Third trimester	1.40(1.38,1.41)	1.38(1.36,1.40)	1.21(1.18,1.24)
Cephalosporin	1.35(1.32,1.37)	1.35(1.33,1.38)	1.13(1.09,1.16)
First trimester	1.34(1.30,1.38)	1.35(1.29,1.40)	1.11(1.05,1.18)
Second trimester	1.43(1.39,1.48)	1.44(1.39,1.50)	1.22(1.15,1.30)
Second or third trimester	1.34(1.31,1.36)	1.35(1.32,1.38)	1.13(1.09,1.17)
Third trimester	1.29(1.26,1.32)	1.29(1.26,1.33)	1.08(1.04,1.13)
Sulfa	1.24(1.20,1.29)	1.23(1.17,1.28)	1.10(1.02,1.18)
First trimester	1.12(1.03,1.22)	1.10(0.99,1.22)	1.04(0.89,1.22)
Second trimester	1.32(1.21,1.44)	1.35(1.22,1.49)	1.08(0.92,1.27)
Second or third trimester	1.27(1.22,1.33)	1.26(1.20,1.33)	1.11(1.03,1.20)
Third trimester	1.26(1.20,1.32)	1.23(1.16,1.31)	1.12(1.02,1.22)
Macrolides	1.36(1.32,1.40)	1.32(1.28,1.37)	1.21(1.15,1.27)
First trimester	1.29(1.21,1.37)	1.22(1.13,1.32)	1.19(1.07,1.33)
Second trimester	1.36(1.29,1.44)	1.39(1.30,1.49)	1.09(0.98,1.21)
Second or third trimester	1.37(1.33,1.41)	1.34(1.29,1.39)	1.21(1.15,1.27)
Third trimester	1.37(1.33,1.42)	1.32(1.27,1.38)	1.25(1.18,1.33)

Table 3: Association (hazard ratio [95% confidence interval]) between child's first exposure to antibiotics and development of atopic dermatitis. Fully adjusted model covariates include maternal atopic dermatitis, maternal exposure to antibiotics, gender assigned at birth of the child, child OAI, Townsend's index, and ethnicity.

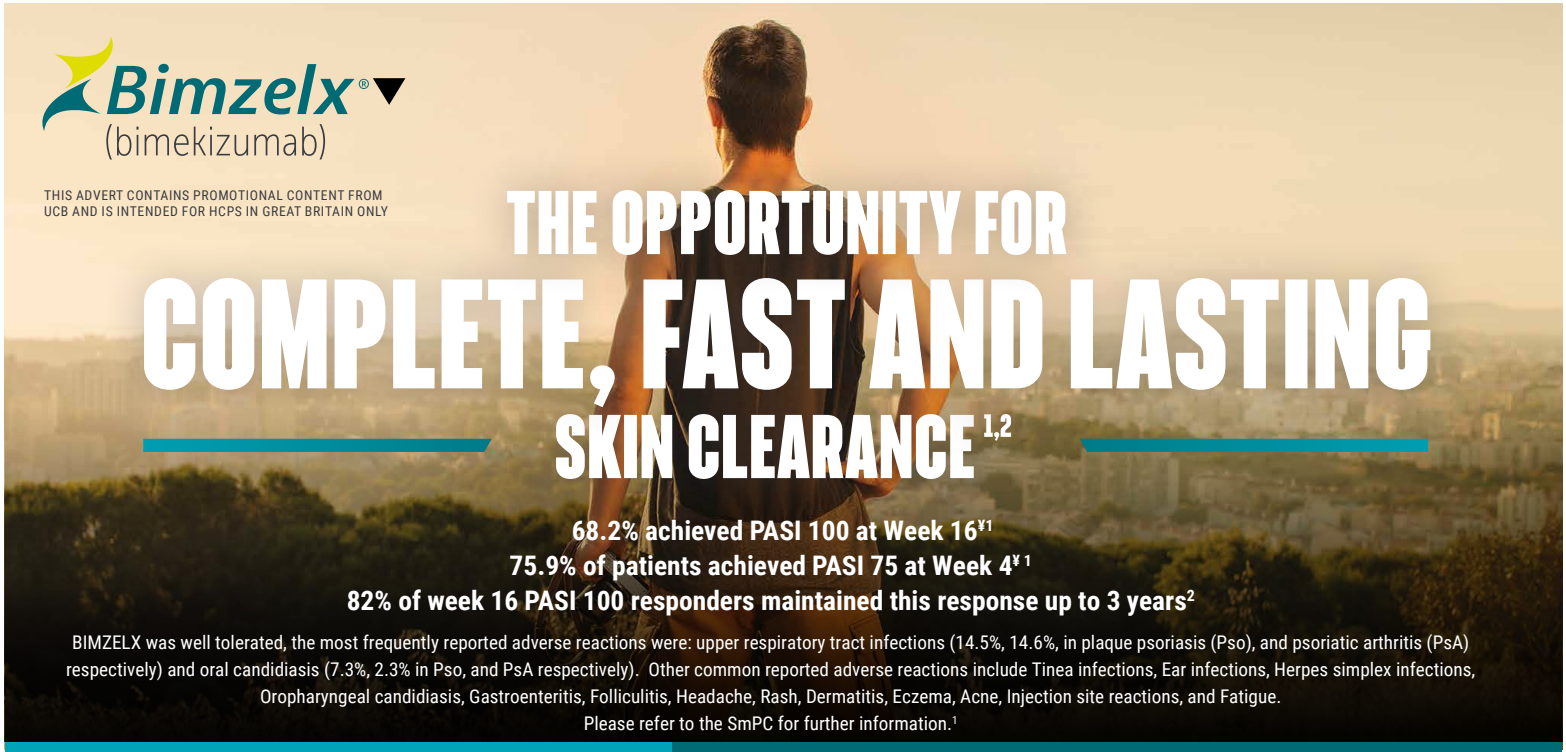
	Penicillin N=701,966(68.6%)	Macrolides N=259,159(25.3%)	Cephalosporin N=99,539(9.7%)	Sulfa N=135,291(13.2%)
Unadjusted	1.81(1.79,1.82)	1.54(1.52,1.56)	1.44(1.41,1.46)	1.43(1.40,1.46)
Maternal atopic dermatitis	1.74(1.72,1.76)	1.48(1.46,1.50)	1.38(1.36,1.41)	1.38(1.36,1.41)
Maternal antibiotic exposure during pregnancy	1.74(1.73,1.76)	1.47(1.45,1.49)	1.36(1.34,1.39)	1.37(1.365,1.40)
Fully adjusted model	1.76(1.75,1.78)	1.52(1.50,1.54)	1.42(1.39,1.44)	1.43(1.40,1.46)

Table 4: Associations (hazard ratio [95% confidence interval]) between antibiotic use within the first 90 days of life and the development of atopic dermatitis. Fully adjusted models* used the following covariates maternal atopic dermatitis (full cohort only), maternal exposure to antibiotics, gender assigned at birth of the child, child's OAI, Townsend's index, and ethnicity.

	Fully cohort	Full cohort*	Mother no AD*	Mother with AD*
Penicillin	1.70(1.67,1.73)	1.76(1.72,1.80)	1.71(1.68,1.75)	1.45(1.40,1.50)
Sulfa	1.46(1.37,1.56)	1.42(1.31,1.53)	1.49(1.39,1.61)	1.24(1.09,1.41)
Cephalosporin	1.70(1.56,1.85)	1.96(1.76,2.18)	1.68(1.52,1.86)	1.53(1.31,1.78)
Macrolide	1.77(1.69,1.86)	1.86(1.75,1.98)	1.81(1.71,1.92)	1.42(1.30,1.56)

Bimzelx® ▼
(bimekizumab)

THIS ADVERT CONTAINS PROMOTIONAL CONTENT FROM UCB AND IS INTENDED FOR HCPS IN GREAT BRITAIN ONLY



THE OPPORTUNITY FOR COMPLETE, FAST AND LASTING SKIN CLEARANCE [1,2]

68.2% achieved PASI 100 at Week 16[¥1]
75.9% of patients achieved PASI 75 at Week 4[¥1]
82% of week 16 PASI 100 responders maintained this response up to 3 years[2]

BIMZELX was well tolerated, the most frequently reported adverse reactions were: upper respiratory tract infections (14.5%, 14.6%, in plaque psoriasis (Pso), and psoriatic arthritis (PsA) respectively) and oral candidiasis (7.3%, 2.3% in Pso, and PsA respectively). Other common reported adverse reactions include Tinea infections, Ear infections, Herpes simplex infections, Oropharyngeal candidiasis, Gastroenteritis, Folliculitis, Headache, Rash, Dermatitis, Eczema, Acne, Injection site reactions, and Fatigue.
Please refer to the SmPC for further information.[1]

Challenge expectations in plaque psoriasis[1,2]

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Footnotes: ¥co-primary endpoints PASI 90 and IGA 0/1 at Week 16
Pso - Plaque Psoriais; PsA - Psoriatic Athritis

BIMZELX® (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Please refer to the SmPC for further information.[1]

PRESCRIBING INFORMATION FOR HCP'S IN GREAT BRITAIN

BIMZELX® ▼ (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy; and for active psoriasis arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs), alone or in combination with methotrexate.[1] (Please consult the Summary of Product Characteristics (SmPC) before prescribing).

Active Ingredient: Bimekizumab – solution for injection in pre-filled syringe or pre-filled pen: *160 mg of bimekizumab in 1 mL of solution (160mg/mL)*. **Indications:** Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Alone or in combination with methotrexate, for active psoriatic arthritis in adults who have had an inadequate response or intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy. **Dosage and Administration:** Should be initiated and supervised by a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated. **Recommended dose:** Plaque Psoriasis: 320 mg (given as two subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. Psoriatic arthritis: 160 mg (given as 1 subcutaneous injection of 160 mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis. After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg every 4 weeks can be considered. Axial spondyloarthritis (nr-axSpA and AS): 160 mg (given as 1 subcutaneous injection) every 4 weeks. For patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Consider discontinuing if no improvement by 16 weeks of treatment. Renal or hepatic impairment: No dose adjustment needed. Elderly: No dose adjustment needed. Administer by subcutaneous injection to thigh, abdomen or upper arm. Rotate injection sites and do not inject into psoriatic plaques or skin that is tender, bruised, erythematous or indurated. Do not shake pre-filled syringe or pre-filled pen. Patients may be trained to self-inject. **Contraindications:** Hypersensitivity to bimekizumab or any excipient; Clinically important active infections (e.g. active tuberculosis). **Warnings and Precautions:** Record name and batch number of administered product. *Infection:* Bimekizumab may increase the risk of infections e.g. upper respiratory tract infections, oral candidiasis. Caution when considering use in patients with a chronic infection or a history of recurrent infection. Must not be initiated if any clinically important active infection until infection resolves or is adequately treated. Advise patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops an infection, the patient should be carefully monitored. If the infection becomes serious or is not responding to standard therapy do not administer bimekizumab until infection resolves. *TB:* Evaluate for TB infection prior to initiating bimekizumab – do not give if active TB. While on bimekizumab, monitor for signs and symptoms of active TB. Consider anti-TB therapy prior to bimekizumab initiation if past history of latent or active TB in whom adequate treatment course cannot be confirmed. *Inflammatory bowel disease:* Bimekizumab is not recommended in patients with inflammatory bowel disease. Cases of new or exacerbations of inflammatory bowel disease have been reported. If inflammatory bowel disease signs/symptoms develop or patient experiences exacerbation of pre-existing inflammatory bowel disease, discontinue bimekizumab and initiate medical management. *Hypersensitivity:* Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, discontinue immediately and treat. *Vaccinations:* Complete all age appropriate immunisations prior to bimekizumab initiation. Do not give live vaccines to bimekizumab patients. Patients may receive inactivated or non-live vaccinations. **Interactions:** A clinically relevant effect on CYP450 substrates with a narrow therapeutic index in which the dose is individually adjusted e.g. warfarin, cannot be excluded. Therapeutic monitoring should be considered. **Fertility, pregnancy and lactation:** Women of child-bearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment. Avoid use of bimekizumab during pregnancy. It is unknown whether bimekizumab is excreted in human milk, hence a risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bimzelx therapy. No data available on human fertility. **Driving and use of machines:** No or negligible influence on ability to drive and use machines. **Adverse Effects:** Refer to SmPC for full information. Very Common *(≥ 1/10):* upper respiratory tract infection; Common *(≥ 1/100 to < 1/10):* oral candidiasis, tinea infections, ear infections, herpes simplex infections, oropharyngeal candidiasis, gastroenteritis, folliculitis; headache, rash, dermatitis and eczema, acne, injection site reactions, fatigue; Uncommon *(≥ 1/1,000 to < 1/100):* mucosal and cutaneous candidiasis (including oesophageal candidiasis), conjunctivitis, neutropenia, inflammatory bowel disease. Storage precautions: Store in a refrigerator (2°C – 8°C), do not freeze. Keep in outer carton to protect from light. Bimzelx can be kept at up to 25°C for a single period of maximum 25 days with protection from light. Product should be discarded after this period or by the expiry date, whichever occurs first.

Legal Category: POM
Marketing Authorisation Numbers: PLGB 00039/0802 (Pre-filled Syringe), PLGB 00039/0803 (Pre-filled Pen).
UK NHS Costs: £2,443 per pack of 2 pre-filled syringes or pens of 160 mg each.
Marketing Authorisation Holder: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE, United Kingdom.
Further information is available from: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 0800 2793177 Email: ucbcares.uk@ucb.com
Date of Revision: August 2023 (GB-P-BK-AS-2300047)
Bimzelx is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard. Adverse events should also be reported to UCB Pharma Ltd at ucbcares.uk@ucb.com or 0800 2793177.

References: 1. BIMZELX (bimekizumab) SmPC. Available at: https://www.medicines.org.uk/emc/product/12834/smpc. Accessed September 2023 **2.** Strober et al. [BE BRIGHT open label extension] Br J Dermatol. 2023. 188(6): 749-759.

GB-BK-2300081 Date of preparation: September 2023.

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