

Specific Adverse Events  
(Safety Analysis Population)

|   | Placebo<br>n | Xanomeline<br>Low Dose<br>n | Xanomeline<br>High Dose<br>n |
|---|--------------|-----------------------------|------------------------------|
| Participants in population                        | 86           | 84                          | 84                           |
| <b>CARDIAC DISORDERS</b>                          |              |                             |                              |
| Atrial Fibrillation                               | 1            | 1                           | 3                            |
| Atrial Flutter                                    | 0            | 1                           | 1                            |
| Atrial Hypertrophy                                | 1            | 0                           | 0                            |
| Atrioventricular Block First Degree               | 1            | 1                           | 0                            |
| Atrioventricular Block Second Degree              | 2            | 0                           | 3                            |
| Bradycardia                                       | 1            | 0                           | 0                            |
| Bundle Branch Block Left                          | 1            | 0                           | 0                            |
| Bundle Branch Block Right                         | 1            | 1                           | 0                            |
| Cardiac Disorder                                  | 0            | 0                           | 1                            |
| Cardiac Failure Congestive                        | 1            | 0                           | 0                            |
| Myocardial Infarction                             | 4            | 2                           | 4                            |
| Palpitations                                      | 0            | 2                           | 0                            |
| Sinus Arrhythmia                                  | 1            | 0                           | 0                            |
| Sinus Bradycardia                                 | 2            | 7                           | 8                            |
| Supraventricular Extrasystoles                    | 1            | 1                           | 1                            |
| Supraventricular Tachycardia                      | 0            | 1                           | 0                            |
| Tachycardia                                       | 1            | 0                           | 0                            |
| Ventricular Extrasystoles                         | 0            | 2                           | 1                            |
| Ventricular Hypertrophy                           | 1            | 0                           | 0                            |
| Wolff-Parkinson-White Syndrome                    | 0            | 1                           | 0                            |
| <b>CONGENITAL, FAMILIAL AND GENETIC DISORDERS</b> |              |                             |                              |
| Ventricular Septal Defect                         | 0            | 1                           | 2                            |
| <b>EAR AND LABYRINTH DISORDERS</b>                |              |                             |                              |
| Cerumen Impaction                                 | 0            | 1                           | 0                            |
| Ear Pain  | 1            | 0                           | 0                            |
| Tinnitus  | 0            | 1                           | 0                            |
| Vertigo   | 0            | 1                           | 1                            |
| <b>EYE DISORDERS</b>                              |              |                             |                              |
| Conjunctival Haemorrhage                          | 0            | 1                           | 0                            |
| Conjunctivitis                                    | 2            | 0                           | 0                            |
| Eye Allergy                                       | 1            | 0                           | 0                            |
| Eye Pruritus                                      | 1            | 0                           | 0                            |
| Eye Swelling                                      | 1            | 0                           | 0                            |
| Glaucoma  | 1            | 0                           | 0                            |

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| Vision Blurred  | 0            | 1                           | 1                            |
| <b>GASTROINTESTINAL DISORDERS</b>                               |              |                             |                              |
| Abdominal Discomfort  | 0            | 0                           | 1                            |
| Abdominal Pain  | 1            | 3                           | 1                            |
| Constipation  | 1            | 0                           | 0                            |
| Diarrhoea   | 9            | 5                           | 4                            |
| Dyspepsia   | 1            | 1                           | 1                            |
| Dysphagia   | 0            | 1                           | 0                            |
| Flatulence  | 1            | 0                           | 0                            |
| Gastrointestinal Haemorrhage                                    | 0            | 0                           | 1                            |
| Gastrooesophageal Reflux Disease                                | 1            | 0                           | 0                            |
| Glossitis   | 1            | 0                           | 0                            |
| Hiatus Hernia   | 1            | 0                           | 0                            |
| Nausea  | 3            | 3                           | 6                            |
| Rectal Haemorrhage  | 0            | 1                           | 0                            |
| Salivary Hypersecretion   | 0            | 0                           | 4                            |
| Stomach Discomfort  | 0            | 0                           | 1                            |
| Vomiting  | 3            | 3                           | 7                            |
| <b>GENERAL DISORDERS AND ADMINISTRATION SITE<br/>CONDITIONS</b> |              |                             |                              |
| Application Site Bleeding                                       | 0            | 1                           | 0                            |
| Application Site Dermatitis                                     | 5            | 9                           | 7                            |
| Application Site Desquamation                                   | 0            | 1                           | 0                            |
| Application Site Discharge                                      | 0            | 0                           | 1                            |
| Application Site Discolouration                                 | 0            | 1                           | 0                            |
| Application Site Erythema                                       | 3            | 12                          | 15                           |
| Application Site Induration                                     | 1            | 0                           | 0                            |
| Application Site Irritation                                     | 3            | 9                           | 9                            |
| Application Site Pain   | 0            | 0                           | 2                            |
| Application Site Perspiration                                   | 0            | 0                           | 2                            |
| Application Site Pruritus                                       | 6            | 22                          | 22                           |
| Application Site Reaction                                       | 1            | 0                           | 1                            |
| Application Site Swelling                                       | 0            | 1                           | 2                            |
| Application Site Urticaria                                      | 0            | 2                           | 1                            |
| Application Site Vesicles                                       | 1            | 4                           | 6                            |
| Application Site Warmth   | 0            | 1                           | 0                            |
| Asthenia  | 1            | 0                           | 1                            |

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|-----------------------------------|--------------|-----------------------------|------------------------------|
| Chest Discomfort                  | 0            | 0                           | 2                            |
| Chest Pain                        | 0            | 0                           | 2                            |
| Chills                            | 1            | 1                           | 1                            |
| Cyst                              | 0            | 1                           | 0                            |
| Fatigue                           | 1            | 5                           | 5                            |
| Feeling Abnormal                  | 0            | 0                           | 1                            |
| Feeling Cold                      | 0            | 0                           | 1                            |
| Inflammation                      | 0            | 1                           | 0                            |
| Malaise                           | 0            | 1                           | 2                            |
| Oedema                            | 0            | 2                           | 0                            |
| Oedema Peripheral                 | 2            | 1                           | 2                            |
| Pain                              | 0            | 1                           | 1                            |
| Pyrexia                           | 2            | 0                           | 1                            |
| Secretion Discharge               | 0            | 1                           | 0                            |
| Sudden Death                      | 0            | 1                           | 0                            |
| Swelling                          | 0            | 1                           | 0                            |
| Ulcer                             | 0            | 1                           | 0                            |
| HEPATOBIILIARY DISORDERS          |              |                             |                              |
| Hyperbilirubinaemia               | 1            | 0                           | 0                            |
| IMMUNE SYSTEM DISORDERS           |              |                             |                              |
| Hypersensitivity                  | 0            | 1                           | 0                            |
| Seasonal Allergy                  | 0            | 0                           | 1                            |
| INFECTIONS AND INFESTATIONS       |              |                             |                              |
| Bronchitis                        | 1            | 0                           | 0                            |
| Cellulitis                        | 0            | 1                           | 0                            |
| Cervicitis                        | 1            | 0                           | 0                            |
| Cystitis                          | 1            | 0                           | 1                            |
| Ear Infection                     | 2            | 0                           | 0                            |
| Gastroenteritis Viral             | 1            | 0                           | 0                            |
| Hordeolum                         | 0            | 0                           | 1                            |
| Influenza                         | 1            | 1                           | 1                            |
| Localised Infection               | 1            | 1                           | 0                            |
| Lower Respiratory Tract Infection | 0            | 0                           | 1                            |
| Nasopharyngitis                   | 2            | 4                           | 6                            |
| Onychomycosis                     | 0            | 1                           | 0                            |
| Pneumonia                         | 0            | 1                           | 0                            |
| Rhinitis                          | 0            | 0                           | 1                            |

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| Upper Respiratory Tract Infection              | 6            | 1                           | 3                            |
| Urinary Tract Infection                        | 2            | 0                           | 1                            |
| Vaginal Mycosis                                | 1            | 0                           | 0                            |
| Viral Infection                                | 0            | 1                           | 0                            |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS |              |                             |                              |
| Contusion                                      | 1            | 1                           | 2                            |
| Excoriation                                    | 2            | 1                           | 1                            |
| Facial Bones Fracture                          | 0            | 0                           | 1                            |
| Fall   | 1            | 2                           | 1                            |
| Hip Fracture                                   | 1            | 0                           | 2                            |
| Joint Dislocation                              | 0            | 1                           | 0                            |
| Skin Laceration                                | 1            | 2                           | 0                            |
| Wound  | 0            | 1                           | 0                            |
| INVESTIGATIONS                                 |              |                             |                              |
| Biopsy   | 0            | 0                           | 1                            |
| Biopsy Prostate                                | 0            | 0                           | 1                            |
| Blood Alkaline Phosphatase Increased           | 1            | 0                           | 0                            |
| Blood Cholesterol Increased                    | 0            | 0                           | 1                            |
| Blood Creatine Phosphokinase Increased         | 1            | 0                           | 0                            |
| Blood Glucose Increased                        | 0            | 1                           | 1                            |
| Blood Urine Present                            | 1            | 0                           | 0                            |
| Body Temperature Increased                     | 0            | 1                           | 0                            |
| Cystoscopy                                     | 1            | 0                           | 0                            |
| Electrocardiogram St Segment Depression        | 4            | 1                           | 0                            |
| Electrocardiogram T Wave Amplitude Decreased   | 1            | 1                           | 0                            |
| Electrocardiogram T Wave Inversion             | 2            | 1                           | 1                            |
| Heart Rate Increased                           | 1            | 0                           | 0                            |
| Heart Rate Irregular                           | 1            | 0                           | 0                            |
| Nasal Mucosa Biopsy                            | 0            | 1                           | 0                            |
| Neutrophil Count Increased                     | 0            | 1                           | 0                            |
| Urine Analysis Abnormal                        | 0            | 1                           | 0                            |
| Weight Decreased                               | 0            | 0                           | 1                            |
| White Blood Cell Count Increased               | 0            | 1                           | 0                            |
| METABOLISM AND NUTRITION DISORDERS             |              |                             |                              |
| Decreased Appetite                             | 1            | 0                           | 1                            |
| Dehydration                                    | 1            | 0                           | 0                            |
| Diabetes Mellitus                              | 1            | 0                           | 0                            |

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|--|--------------|-----------------------------|------------------------------|
| Food Craving   | 1            | 1                           | 0                            |
| Hypercholesterolaemia  | 0            | 0                           | 1                            |
| Hyponatraemia  | 1            | 0                           | 0                            |
| Increased Appetite   | 1            | 0                           | 1                            |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE<br>DISORDERS                     |              |                             |                              |
| Arthralgia   | 1            | 2                           | 1                            |
| Arthritis  | 1            | 0                           | 1                            |
| Back Pain  | 1            | 1                           | 3                            |
| Flank Pain   | 0            | 0                           | 2                            |
| Muscle Spasms  | 0            | 1                           | 1                            |
| Muscular Weakness  | 0            | 1                           | 0                            |
| Myalgia  | 0            | 0                           | 1                            |
| Pain In Extremity  | 1            | 0                           | 0                            |
| Shoulder Pain  | 1            | 2                           | 0                            |
| NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED<br>(INCL CYSTS AND POLYPS) |              |                             |                              |
| Colon Cancer   | 0            | 1                           | 0                            |
| Malignant Fibrous Histiocytoma   | 0            | 1                           | 0                            |
| Prostate Cancer  | 0            | 0                           | 1                            |
| NERVOUS SYSTEM DISORDERS   |              |                             |                              |
| Amnesia  | 0            | 0                           | 1                            |
| Balance Disorder   | 0            | 1                           | 0                            |
| Burning Sensation  | 0            | 0                           | 2                            |
| Cognitive Disorder   | 0            | 0                           | 1                            |
| Complex Partial Seizures   | 0            | 1                           | 0                            |
| Coordination Abnormal  | 0            | 1                           | 0                            |
| Dizziness  | 2            | 8                           | 12                           |
| Headache   | 7            | 3                           | 6                            |
| Hemianopia Homonymous  | 0            | 1                           | 0                            |
| Hypersomnia  | 0            | 0                           | 1                            |
| Lethargy   | 0            | 1                           | 1                            |
| Paraesthesia   | 0            | 0                           | 1                            |
| Paraesthesia Oral  | 0            | 1                           | 0                            |
| Parkinson'S Disease  | 1            | 0                           | 0                            |
| Parosmia   | 0            | 0                           | 1                            |
| Partial Seizures With Secondary Generalisation                         | 0            | 0                           | 1                            |
| Psychomotor Hyperactivity  | 1            | 0                           | 0                            |

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|---|--------------|-----------------------------|------------------------------|
| Somnolence                                      | 2            | 3                           | 1                            |
| Stupor  | 0            | 1                           | 0                            |
| Syncope   | 0            | 4                           | 3                            |
| Syncope Vasovagal                               | 0            | 0                           | 1                            |
| Transient Ischaemic Attack                      | 0            | 2                           | 1                            |
| PSYCHIATRIC DISORDERS                           |              |                             |                              |
| Agitation                                       | 2            | 2                           | 1                            |
| Anxiety   | 1            | 3                           | 0                            |
| Completed Suicide                               | 1            | 0                           | 0                            |
| Confusional State                               | 2            | 3                           | 1                            |
| Delirium  | 0            | 0                           | 1                            |
| Delusion  | 1            | 0                           | 1                            |
| Depressed Mood                                  | 0            | 1                           | 1                            |
| Disorientation                                  | 1            | 0                           | 0                            |
| Hallucination                                   | 0            | 0                           | 1                            |
| Hallucination, Visual                           | 0            | 0                           | 1                            |
| Insomnia  | 2            | 0                           | 2                            |
| Irritability                                    | 1            | 1                           | 0                            |
| Libido Decreased                                | 0            | 0                           | 1                            |
| Listless  | 0            | 0                           | 1                            |
| Nightmare                                       | 0            | 0                           | 1                            |
| Restlessness                                    | 0            | 1                           | 0                            |
| RENAL AND URINARY DISORDERS                     |              |                             |                              |
| Calculus Urethral                               | 0            | 0                           | 1                            |
| Dysuria   | 1            | 1                           | 0                            |
| Enuresis  | 0            | 1                           | 0                            |
| Incontinence                                    | 0            | 1                           | 0                            |
| Micturition Urgency                             | 1            | 1                           | 1                            |
| Nephrolithiasis                                 | 1            | 0                           | 1                            |
| Pollakiuria                                     | 1            | 0                           | 0                            |
| REPRODUCTIVE SYSTEM AND BREAST DISORDERS        |              |                             |                              |
| Benign Prostatic Hyperplasia                    | 1            | 0                           | 1                            |
| Pelvic Pain                                     | 1            | 0                           | 0                            |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS |              |                             |                              |
| Allergic Granulomatous Angiitis                 | 0            | 0                           | 1                            |
| Cough   | 3            | 6                           | 5                            |
| Dysphonia                                       | 0            | 1                           | 0                            |

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|--|--------------|-----------------------------|------------------------------|
| Dyspnoea                               | 1            | 1                           | 1                            |
| Emphysema                              | 1            | 0                           | 0                            |
| Epistaxis                              | 0            | 1                           | 2                            |
| Haemoptysis                            | 1            | 0                           | 0                            |
| Nasal Congestion                       | 3            | 1                           | 3                            |
| Pharyngeal Erythema                    | 0            | 0                           | 1                            |
| Pharyngolaryngeal Pain                 | 0            | 1                           | 1                            |
| Postnasal Drip                         | 1            | 0                           | 0                            |
| Productive Cough                       | 0            | 0                           | 1                            |
| Rales                                  | 1            | 0                           | 0                            |
| Respiratory Tract Congestion           | 0            | 0                           | 1                            |
| Rhinorrhoea                            | 0            | 1                           | 1                            |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS |              |                             |                              |
| Actinic Keratosis                      | 0            | 0                           | 1                            |
| Alopecia                               | 1            | 0                           | 0                            |
| Blister                                | 0            | 5                           | 1                            |
| Cold Sweat                             | 1            | 0                           | 0                            |
| Dermatitis Atopic                      | 1            | 0                           | 0                            |
| Dermatitis Contact                     | 0            | 1                           | 0                            |
| Drug Eruption                          | 1            | 0                           | 0                            |
| Erythema                               | 9            | 15                          | 14                           |
| Hyperhidrosis                          | 2            | 4                           | 8                            |
| Pruritus                               | 8            | 23                          | 26                           |
| Pruritus Generalised                   | 0            | 1                           | 1                            |
| Rash                                   | 5            | 13                          | 11                           |
| Rash Erythematous                      | 0            | 2                           | 0                            |
| Rash Maculo-Papular                    | 0            | 0                           | 1                            |
| Rash Papular                           | 0            | 0                           | 1                            |
| Rash Pruritic                          | 0            | 1                           | 2                            |
| Skin Exfoliation                       | 0            | 1                           | 0                            |
| Skin Irritation                        | 3            | 6                           | 5                            |
| Skin Odour Abnormal                    | 0            | 0                           | 1                            |
| Skin Ulcer                             | 1            | 0                           | 0                            |
| Urticaria                              | 0            | 1                           | 1                            |
| SOCIAL CIRCUMSTANCES                   |              |                             |                              |
| Alcohol Use                            | 0            | 0                           | 1                            |
| SURGICAL AND MEDICAL PROCEDURES        |              |                             |                              |

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| Acrochordon Excision                                 | 0            | 0                           | 1                            |
| Cataract Operation                                   | 1            | 1                           | 0                            |
| Eye Laser Surgery                                    | 1            | 0                           | 0                            |
| Skin Lesion Excision                                 | 0            | 0                           | 1                            |
| VASCULAR DISORDERS                                   |              |                             |                              |
| Hot Flush  | 0            | 1                           | 0                            |
| Hypertension   | 1            | 1                           | 1                            |
| Hypotension  | 2            | 1                           | 0                            |
| Orthostatic Hypotension                              | 1            | 0                           | 0                            |
| Wound Haemorrhage                                    | 0            | 0                           | 1                            |
| Number of participants with specific adverse events. |              |                             |                              |

Source: ADSL and ADAE datasets