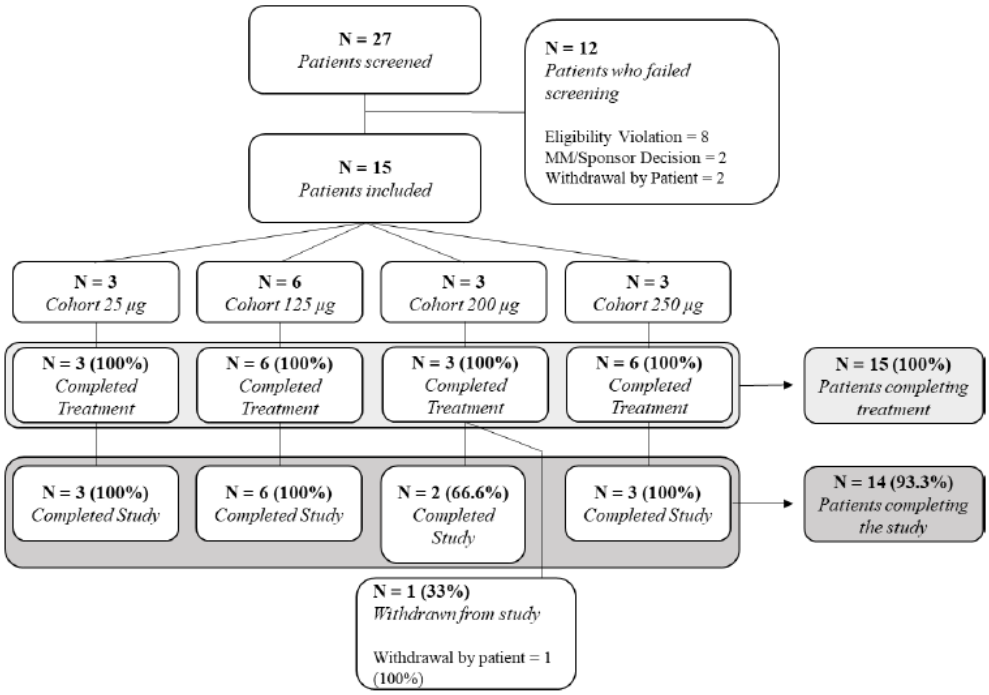
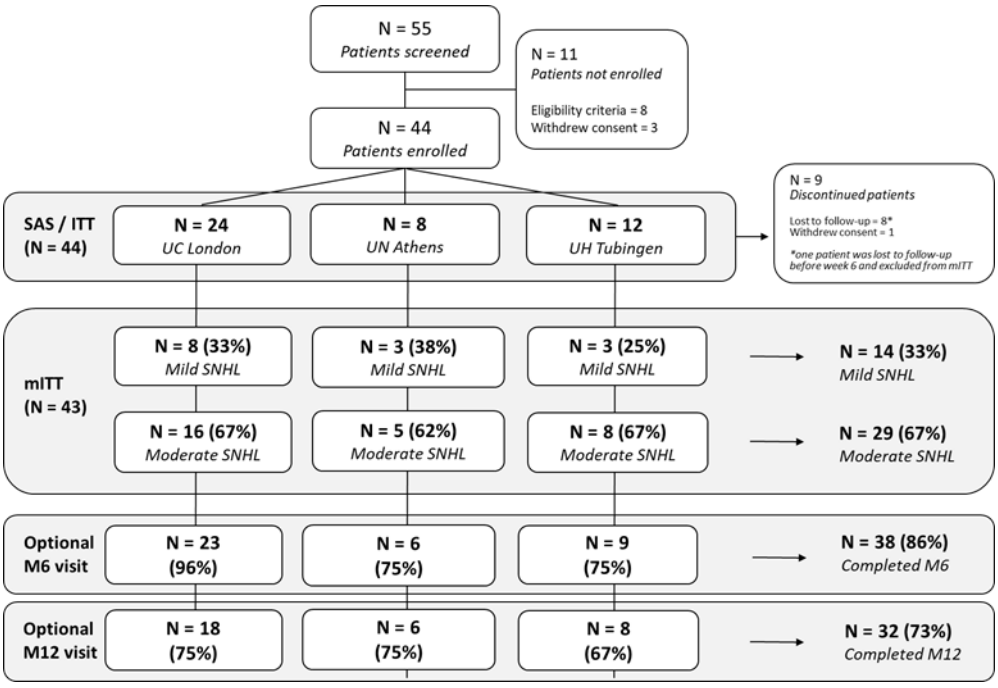
- **Title of Study:** A Phase I/II multiple ascending dose open-label safety and efficacy study of the Notch Inhibitor LY3056480 in patients with mild to moderate sensorineural hearing loss (ISRCTN59733689)

- **Participant Flow Phase I**



- **Participant Flow Phase IIa**



- **Baseline Characteristics and common Adverse Events**

		Phase I	Phase IIa
Dose level	µg	25, 125, 200, 250	250
Number of participants	N	15	44
Age	Median (years)	60	58
	Min - Max (years)	22 - 79	32 - 73
Gender	Female	7 (46.7%)	15 (34.1%)
	Male	8 (53.3%)	29 (65.9%)
Ethnic group	White	15 (100%)	42 (95.4%)
	Asian	0 (0%)	1 (2.3%)
	Other	0 (0%)	1 (2.3%)
Years of Schooling	Median (years)	16	16
	Min - Max (years)	12 – 20	8 – 24
Education	Primary schooling only	0 (0%)	1 (2.3%)
	Secondary schooling	5 (33.3%)	20 (45.5%)
	Tertiary / higher education	10 (66.7%)	23 (52.3%)
Severity of Hearing Loss	Mild	9 (60%)	14 (33.3%)
	Moderate	6 (40%)	29 (66.7%)
	Mean Pure-Tone HLA 2,4,8 kHz	49.1 ± 12.6 HL	55.3 ± 9.3 HL
Duration of Hearing Loss	Range (yrs)	0-10	0-19
Adverse Events	Injection site pain	10 (66.7%)	39 (88.6%)
	Ear pain	4 (26.7%)	13 (29.5%)
	Ear discomfort	8 (53.3%)	6 (13.6%)
	Procedural pain	4 (26.7%)	11 (25%)
	Decreased hearing	10 (66.7%)	6 (13.6%)
	Tinnitus	12 (80%)	15 (34.1%)
	Dizziness	7 (46.7%)	6 (13.6%)

- **Outcome Measures:**

The primary efficacy endpoint	Average change in hearing from baseline in the treated ear at 12 weeks across three frequencies (2, 4, 8 kHz), as measured by Pure-Tone Audiometry (PTA) (dBHL).
The secondary efficacy endpoints up to week 12	Hearing: -Change from baseline at 6 and 12 weeks (treated ear, untreated ear and difference), in terms of: -Hearing level as tested by PTA (dBHL) at individual frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8, 12.5 and 16 kHz) -Average change in hearing level across three frequencies (2, 4, 8 kHz), as measured by PTA (dBHL) (at 6 weeks only) -Speech audiometry as tested by speech in noise testing to determine signal to noise ratio loss shift -Middle ear immittance as tested by tympanometry and Acoustic Reflex Testing (ART) to determine middle ear pressure, volume and compliance values and acoustic threshold reflex shift -Distortion Product Oto-Acoustic Emissions (DPOAE) – Signal to Noise Ratio (SNR) and absolute levels -Cochlear dead regions as tested by the Threshold Equalising Noise test -Hearing specific quality of life (per patient), as measured by the Hearing Handicap Inventory for Adults/Elderly (HHIA/E) questionnaire

	-Level of tinnitus as measured by the Tinnitus Functional Index (TFI) -Change in Hearing Aid use as measured by the Hearing Aid - Outcome Questionnaire (at month 6 and 12 optional visits) Balance: -Change from baseline at 12 weeks, as measured by a clinical balance assessment, including History and Examination (Eye Movements, Head Thrust, modified Romberg, Unterberger, Bithermal Air Calorics using Videonystagmography [VNG]), and Dizziness Handicap Inventory
Endpoints at 6 and 12 months	Hearing: -Average change in hearing from baseline in the treated ear across three frequencies (2, 4, 8 kHz), as measured by Pure-Tone Audiometry (PTA) (dBHL) -Change from baseline (treated ear, untreated ear and difference), in terms of: Hearing level as tested by PTA (dBHL) at individual frequencies (0.25, 0.5, 1, 2, 3, 4, 6, 8, 12.5 and 16 kHz) -Average change in hearing level across three frequencies (2, 4, 8 kHz), as measured by PTA (dBHL) -Speech audiometry as tested by speech in noise testing to determine signal to noise ratio loss shift -Middle ear immittance as tested by tympanometry -Distortion Product Oto-Acoustic Emissions (DPOAE) – Signal to Noise Ratio (SNR) and absolute levels -Hearing specific quality of life (per patient), as measured by the Hearing Handicap Inventory for Adults/Elderly (HHIA/E) questionnaire -Level of tinnitus as measured by the Tinnitus Functional Index (TFI) -Change in Hearing Aid use as measured by the Hearing Aid Outcome Questionnaire (at month 6 and 12 optional visits) Balance: -Change from baseline at 12 weeks, as measured by a clinical balance assessment
Safety and tolerability endpoints	-Hearing and balance as defined in the above endpoints -Facial nerve function: Change from baseline at the treated side up to month 12, in terms of: Facial nerve function as measured by the House-Brackman grading scale -Taste, as reported by the patient (no change, altered taste, loss of taste) -Occurrence and severity of Investigational Medicinal Product (IMP)-related local and systemic AEs up to 12 months -Occurrence and severity of procedure related local and systemic AEs up to 12 months -Occurrence of systemic AEs as measured by potentially clinically significant changes in Electrocardiogram (ECG), vital signs, physical examinations and laboratory tests up to 12 weeks -Occurrence of injection sites reactions in and around the treated ear as assessed by otomicroscopy up to 12 months