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Risk of Sodium-Associated Negative Clinical Outcomes in Individuals With Idiopathic Hypersomnia in the United States: A Real-World Analysis

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Introduction

- Idiopathic hypersomnia is a rare neurological disorder characterised by excessive daytime sleepiness, sleep inertia, prolonged and unrefreshing sleep, and cognitive dysfunction which can impact all aspects of individuals' lives[1,2]
- Prior research has established an association between idiopathic hypersomnia and an increased prevalence of cardiovascular, cardiometabolic, and renal comorbidities compared with those without idiopathic hypersomnia, which may be exacerbated by excess sodium intake[3-5]

Objective

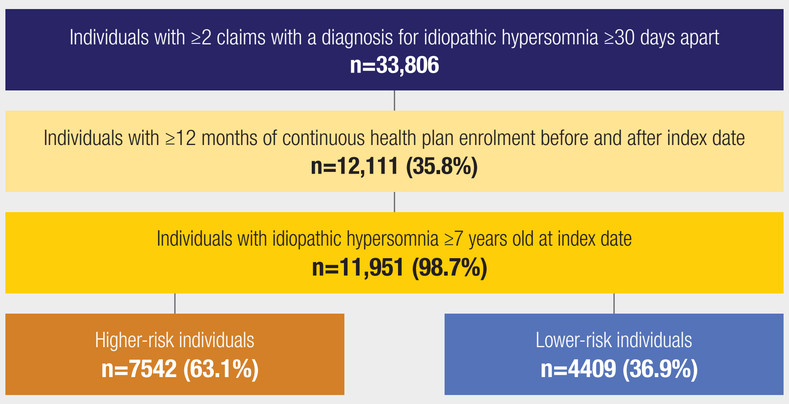
- To describe and compare the risk of developing sodium-associated negative clinical outcomes (NCOs) among individuals with idiopathic hypersomnia compared with those without idiopathic hypersomnia
- To quantify the extent to which risk is further elevated among individuals with pre-existing sodium-associated risk factors

Methods

Study Design and Population

- **Data Source:** Komodo Research Data (KRD+; 01/01/2016–31/01/2024), a large administrative claims database containing data from over 330 million individuals in the United States
- **Study Design:** Retrospective observational cohort study

Figure 1. Study Design

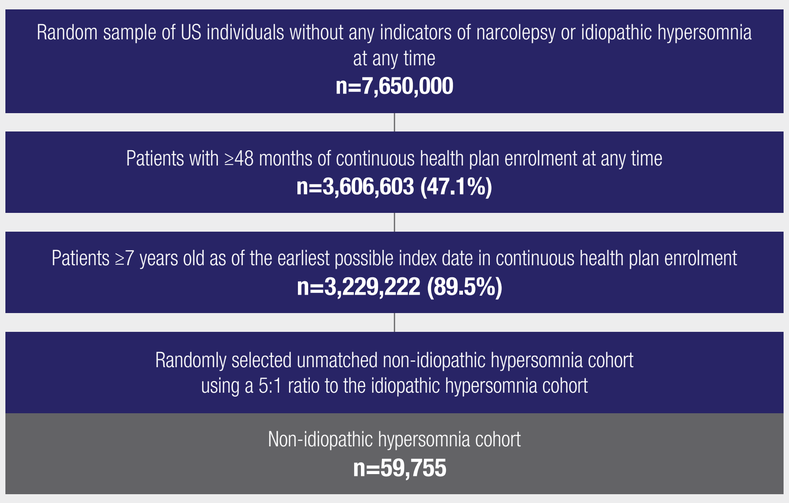


NCO, negative clinical outcome.

- **Study Population**
  - **Idiopathic hypersomnia cohort:** Continuously enrolled individuals aged ≥7 years with ≥2 claims with a diagnosis for idiopathic hypersomnia (*International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM]: G47.11, G47.12) on distinct dates ≥30 days apart
    - *Index date:* First-observed diagnosis of idiopathic hypersomnia
  - **Non-idiopathic hypersomnia cohort:** Individuals aged ≥7 years without narcolepsy or idiopathic hypersomnia (ie, no diagnosis code or oxybate prescription) at any time in the available data
    - *Index date:* Randomly selected date
- Sodium-associated risk factors were assessed in the 12-month baseline period and included cardiovascular, cardiometabolic, and renal conditions; liver cirrhosis; and sleep apnoea
  - Based on risk factors, the IH cohort was stratified into *risk subgroups*:
    - **Higher-risk:** Individuals with ≥1 risk factor pre-index
    - **Lower-risk:** Individuals with no risk factors pre-index

Figure 2. Sample Selection for Idiopathic Hypersomnia Cohort

Figure 3. Sample Selection for Non-Idiopathic Hypersomnia Cohort



Outcomes

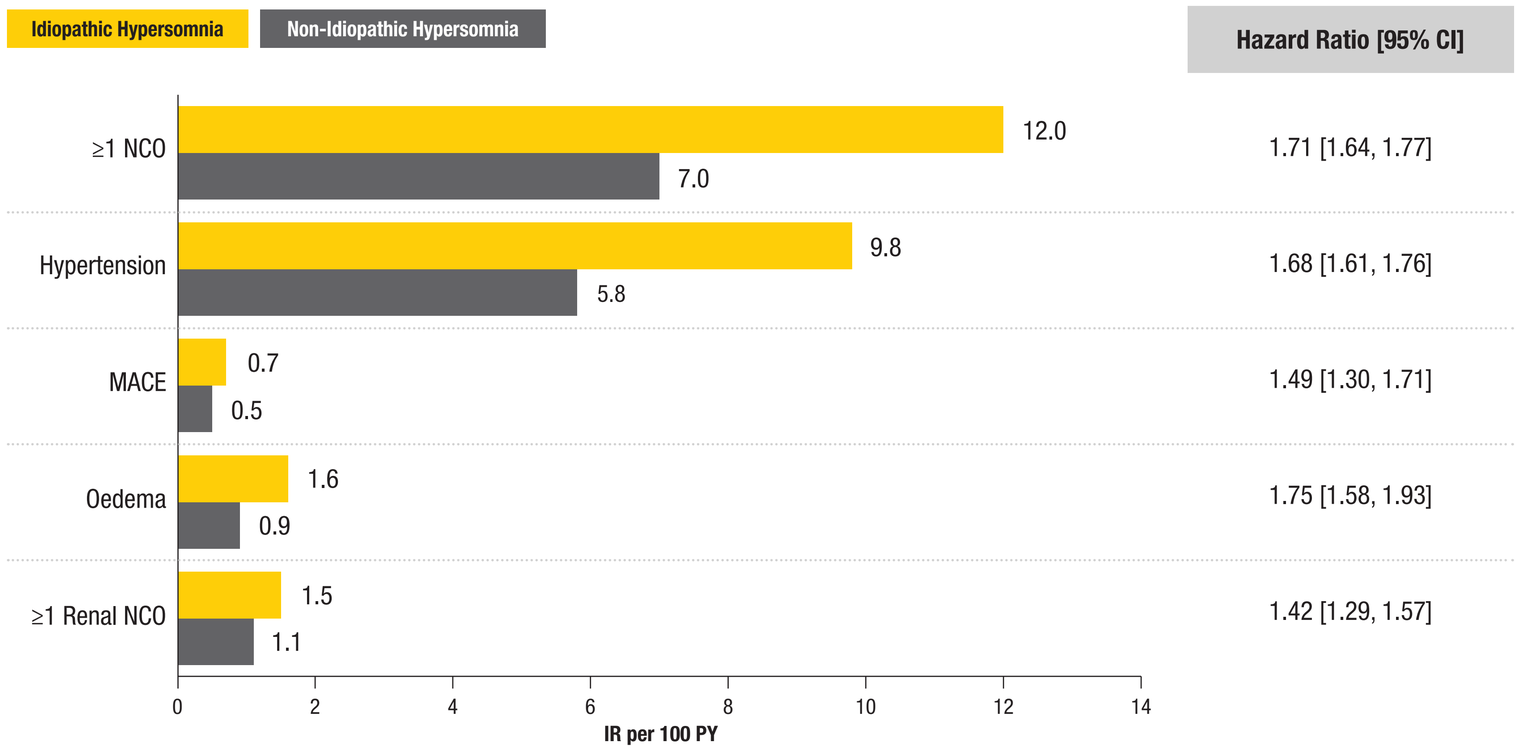
- Primary sodium-associated NCOs were identified through pragmatic literature review and clinical expert discussion, and included the following conditions or events:
  - **Cardiovascular:** Hypertension, heart failure, stroke, transient ischaemic attack, major adverse cardiovascular event (MACE; ie, heart failure, stroke, myocardial infarction, unstable angina, or coronary revascularisation procedures)
  - **Cardiometabolic:** Oedema
  - **Renal:** Proteinuria, chronic kidney disease, kidney failure
- Additional NCOs included a cardiovascular composite outcome (occurrence of atrial fibrillation, atherosclerosis, myocardial infarction, unstable angina, or cardiac arrest), obesity, type 2 diabetes, metabolic syndrome, or sleep apnoea
- The occurrence of new-onset, recurring, or progressing NCOs was measured in the follow-up period using algorithms developed with clinical expert input (see **Supplemental Table 1**, accessed via the QR code in the lower right corner of this poster)

Statistical Analyses

- Demographic characteristics were assessed on the index date
- Entropy balancing was used to balance age, sex, race, health plan type, and year of index date between the idiopathic hypersomnia cohort and the non-idiopathic hypersomnia cohort
  - Weights from entropy balancing were applied to all analyses using the non-idiopathic hypersomnia cohort
- Incidence rates for ≥1 NCO, hypertension, MACE, oedema, and ≥1 renal NCO were calculated per 100 person-years (PY) until the first new onset, recurring, or progressing NCO (event) or end of follow-up (censor)
- Hazard ratios and 95% confidence intervals (CIs) were calculated for each reported NCO using weighted and unweighted Cox proportional hazards models to compare the idiopathic hypersomnia and non-idiopathic hypersomnia cohorts and the risk subgroups within the idiopathic hypersomnia cohort
  - For risk subgroups, a sensitivity analysis was conducted including age as a covariate in the Cox proportional hazards models

Results

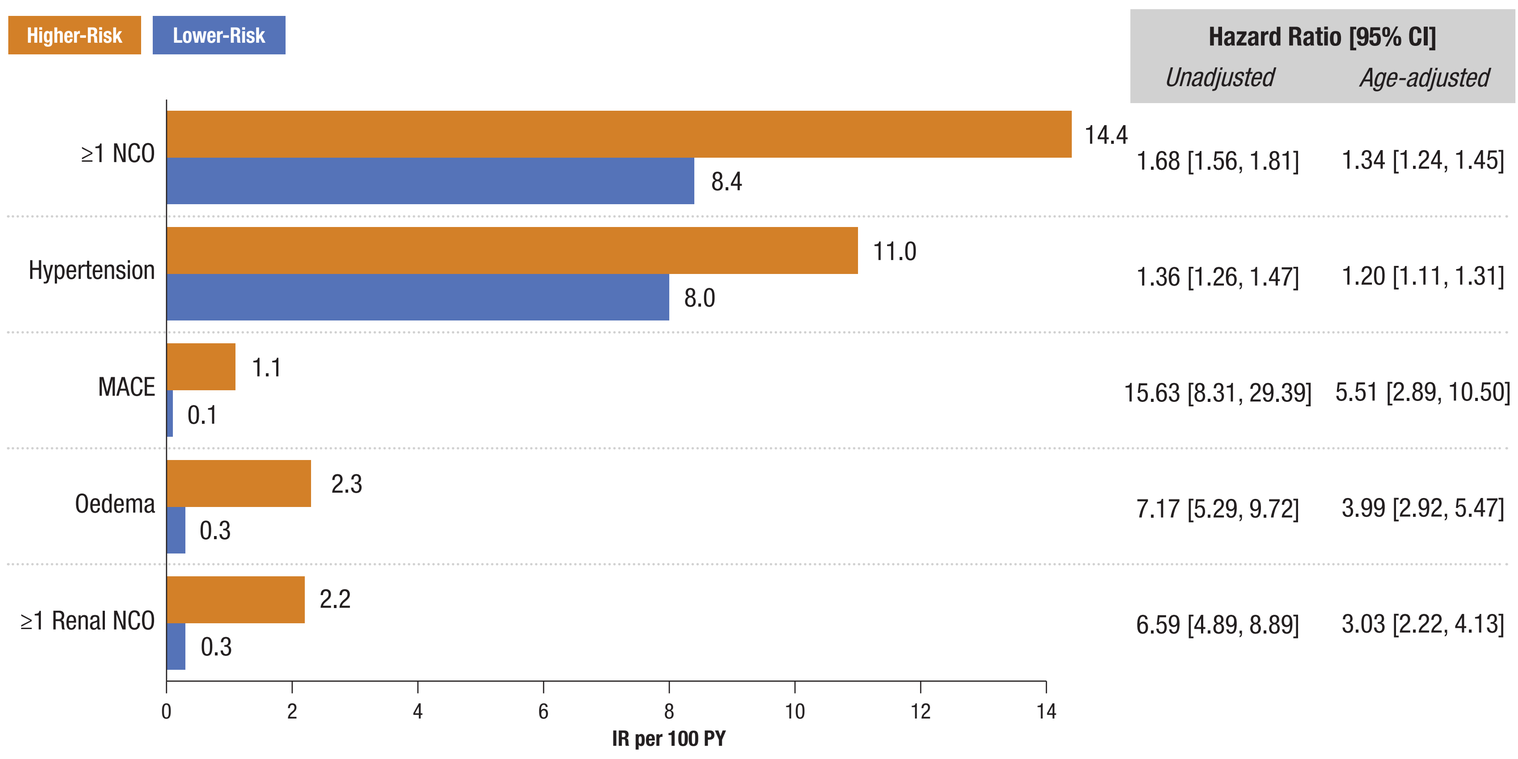
Figure 4. Incidence Rates (per 100 PY) and Hazard Ratios for Primary Negative Clinical Outcomes in Idiopathic Hypersomnia vs Non-Idiopathic Hypersomnia Cohorts



CI, confidence interval; IR, incidence rate; MACE, major adverse cardiovascular event; NCO, negative clinical outcome; PY, person-years.

- Individuals with idiopathic hypersomnia had higher incidence rates and risk of developing all assessed NCOs relative to individuals without idiopathic hypersomnia
  - Incidence rates and risk of having at least 1 NCO were greater in the idiopathic hypersomnia cohort compared with the non-idiopathic hypersomnia cohort
- Among primary NCOs, hazard ratios were highest for oedema and hypertension, for which individuals with idiopathic hypersomnia had a 75% and 68% increased risk, respectively
- Kaplan-Meier curves are presented for primary NCOs in **Supplemental Figures 1–5** and for additional NCOs in **Supplemental Figures 6–10**

Figure 5. Incidence Rates (per 100 PY) and Hazard Ratios for Primary Negative Clinical Outcomes Comparing Higher-Risk vs Lower-Risk Idiopathic Hypersomnia Subgroups



CI, confidence interval, IR, incidence rate; MACE, major adverse cardiovascular event; NCO, negative clinical outcome; PY, person-years.

- Individuals with idiopathic hypersomnia who had at least 1 sodium-related risk factor ("higher-risk individuals") had higher incidence rates and risk of experiencing all assessed NCOs, compared with individuals with idiopathic hypersomnia who were lower-risk
- The elevation in risk varied across primary NCOs, ranging from 36% increased risk of hypertension up to 1563% increased risk of MACE
- Results were attenuated with age adjustment, but risk remained increased for higher-risk individuals
- Kaplan-Meier curves are presented for primary NCOs in **Supplemental Figures 11–15** and for additional NCOs in **Supplemental Figures 16–20**

Table 1. Demographic Characteristics of Idiopathic Hypersomnia and Non-Idiopathic Hypersomnia Cohorts at Baseline

	Idiopathic Hypersomnia Cohort n=11,951	Non-Idiopathic Hypersomnia Cohort n=59,755
Age (years), mean (SD) [median]	**41.7 (15.7) [40.6]**	**41.8 (16.0) [40.7]**
Female, n (%)	**7936 (66.4)**	**39,680 (66.4)**
Race/ethnicity, n (%)		
Known[a]	8463 (70.8)	42,315 (70.8)
White	6862 (81.1)	34,310 (81.1)
Black or African American	616 (7.3)	3080 (7.3)
Asian or Pacific Islander	218 (2.6)	1090 (2.6)
Hispanic or Latino	537 (6.3)	2685 (6.3)
Other	230 (2.7)	1150 (2.7)
Unknown	3488 (29.2)	17,440 (29.2)
Health plan, n (%)		
Commercial	9581 (80.2)	47,905 (80.2)
Medicare	1140 (9.5)	5700 (9.5)
Medicaid	1230 (10.3)	6150 (10.3)

[a]Proportions of patients in each race/ethnicity category were reported among those with known race/ethnicity.
SD, standard deviation.

Conclusions

- Individuals with idiopathic hypersomnia had an elevated risk of developing new-onset or experiencing recurrence or progression of sodium-associated cardiovascular, cardiometabolic, and renal negative clinical outcomes (NCOs) versus individuals without idiopathic hypersomnia
- Many individuals with idiopathic hypersomnia (63.1%) had sodium-associated risk factors prior to their idiopathic hypersomnia diagnosis, for whom the risk of NCOs was particularly heightened
- As laboratory tests and other clinical observations are not available in claims data, new onset, recurring, and progressing NCOs were proxied with algorithms based on diagnosis, procedure, and treatment codes, and were not validated or confirmed with chart notes
- Findings highlight the importance of reducing sodium intake to mitigate the risk of NCOs among individuals with idiopathic hypersomnia, the majority of whom present with pre-existing cardiovascular, cardiometabolic, and renal comorbidities

References: 1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition, Text Revision.* Darien, IL: American Academy of Sleep Medicine; 2023. **2.** Boulanger T, et al. *Sleep Adv.* 2024;5(1):zpae059. **3.** Lillaney, et al. *Neurology.* 2024;102(7_supplement_1):6410. **4.** Saad R, et al. *Sleep Med.* 2023;115:S155-S156. **5.** Saad R, et al. *Sleep Epidemiol.* 2023;3:100059.

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Disclosures: SC Markt, **C Drachenberg**, **JK Alexander**, **M Whalen**, and **S Beaty** are full-time employees of Jazz Pharmaceuticals who, in the course of this employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals, plc. **PR Taub** is a consultant to Amgen, Bayer, Boehringer-Ingelheim, Edwards, Esperion, Jazz Pharmaceuticals, Lilly, Medtronic, Merck, Novartis, Novo Nordisk, and Sanofi. **LA Surkin** is a consultant to Alkermes, Jazz Pharmaceuticals, and Takeda. **K Easson**, **P Gagnon-Sanschagrin**, **R Bellefleur**, **M Levesque-Leroux**, and **A Guérin** are employees of Analysis Group ULC, a consulting company that has provided paid consulting services to Jazz Pharmaceuticals. **RJ Kovacs** is a consultant for Jazz Pharmaceuticals and Lilly, serves on data and safety monitoring boards for Immunovant and Relmada, and is on clinical events committees for Cook and Zydus.

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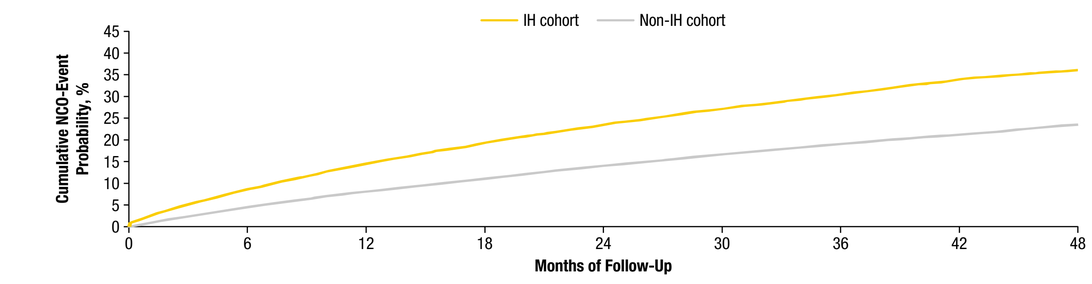
Supplemental Materials

Supplemental Table 1. Operational Definitions for Primary and Additional NCOs

Primary NCOs	Definition
≥1 NCO	Occurrence of a hypertension, MACE, oedema, or renal NCO, as defined below.
Hypertension	An increase in the number of observed anti-hypertensive treatment classes compared with the 12-month baseline period (eg, from 1 treatment class pre-index to 2 treatment classes post-index, etc), or an inpatient admission with a procedure for renal denervation.
MACE	An inpatient admission with a diagnosis for myocardial infarction, stroke/TIA, heart failure, unstable angina, or a procedure for coronary revascularisation, with no inpatient claims with the same diagnosis and/or procedure within 30 days before admission.
Oedema	An escalation in treatment compared with the 12-month baseline period, as defined by the hierarchy below: 1) No observed diuretics 2) Initiation of first oral diuretic (other than loop diuretic) 3) Increase in the number of observed oral diuretic classes 4) Initiation of first oral loop diuretic or metolazone 5) Initiation of an IV or SC diuretic Individuals with an IV/SC diuretic pre-index could not be observed to progress and were not at risk of an oedema NCO.
≥1 renal NCO	An increase in the severity of renal disease compared with the 12-month baseline period, as defined by the hierarchy below: 1) No observed renal disease 2) Proteinuria or CKD stage 1–4 a. Progression to a higher stage of CKD, between stages 1–4, was also considered an NCO if observed 3) CKD stage 5, end-stage renal disease, or dialysis 4) Renal transplant (or repeat renal transplant)
Additional NCOs	**Definition**
CV composite NCO	Occurrence of an atrial fibrillation, atherosclerosis, myocardial infarction, unstable angina, or cardiac arrest NCO. An atrial fibrillation NCO was defined as an interventional procedure with a diagnosis for atrial fibrillation; an increase in the number of treatment classes used for atrial fibrillation compared with the 12-month baseline period; or an inpatient admission with a diagnosis for atrial fibrillation, with no inpatient claims with the same diagnosis within 30 days before admission. An atherosclerosis NCO was defined as an interventional procedure with a diagnosis for atherosclerosis. Myocardial infarction, unstable angina, and cardiac arrest NCOs were defined as an inpatient admission with a diagnosis for myocardial infarction, unstable angina, or cardiac arrest, respectively, with no inpatient claims with the same diagnosis within 30 days before admission.
Obesity	New onset of obesity, defined as ≥2 diagnoses for obesity on distinct dates. Individuals with obesity in the 12-month baseline period were not at risk of an obesity NCO.
Type 2 diabetes	An escalation in treatment compared with the 12-month baseline period, as defined by the hierarchy below: 1) An increase in the number of observed anti-diabetic treatment classes compared with the 12-month baseline period 2) Initiation of insulin Individuals with insulin use pre-index could not be observed to progress and were not at risk of a type 2 diabetes NCO.
Metabolic syndrome	New onset of metabolic syndrome, defined as ≥2 diagnoses for metabolic syndrome on distinct dates. Individuals with metabolic syndrome in the 12-month baseline period were not at risk of a metabolic syndrome NCO.
Sleep apnoea	New onset of sleep apnoea, defined as ≥2 diagnoses for sleep apnoea on distinct dates. Individuals with sleep apnoea in the 12-month baseline period were not at risk of a sleep apnoea NCO.

CKD, chronic kidney disease; CV, cardiovascular; IV, intravenous; MACE, major adverse cardiovascular event; NCO, negative clinical outcome; SC, subcutaneous; TIA, transient ischaemic attack.

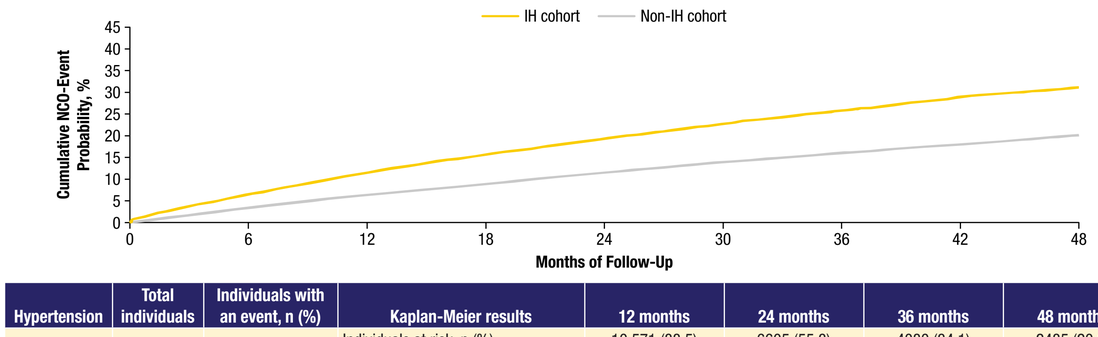
Supplemental Figure 1. Kaplan-Meier Analyses for ≥1 NCO[a]: IH vs Non-IH Cohorts



≥1 NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,951**	**3586 (30.0)**	Individuals at risk, n (%)	10,217 (85.5)	6254 (52.3)	3823 (32.0)	2311 (19.3)
			Cumulative number of events, n (%)	1734 (14.5)	2636 (22.1)	3115 (26.1)	3375 (28.2)
			Cumulative probability, % (95% CI)	14.5 (13.9, 15.2)	23.5 (22.7, 24.3)	30.5 (29.6, 31.4)	36.1 (35.0, 37.2)
Non-IH cohort	**59,755**	**11,468 (19.2)**	Individuals at risk, n (%)	54,918 (91.9)	36,734 (61.5)	21,795 (36.5)	12,414 (20.8)
			Cumulative number of events, n (%)	4836 (8.1)	7916 (13.2)	9675 (16.2)	10,607 (17.8)
			Cumulative probability, % (95% CI)	8.1 (7.8, 8.4)	14.0 (13.7, 14.4)	19.1 (18.7, 19.5)	23.5 (23.0, 24.1)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

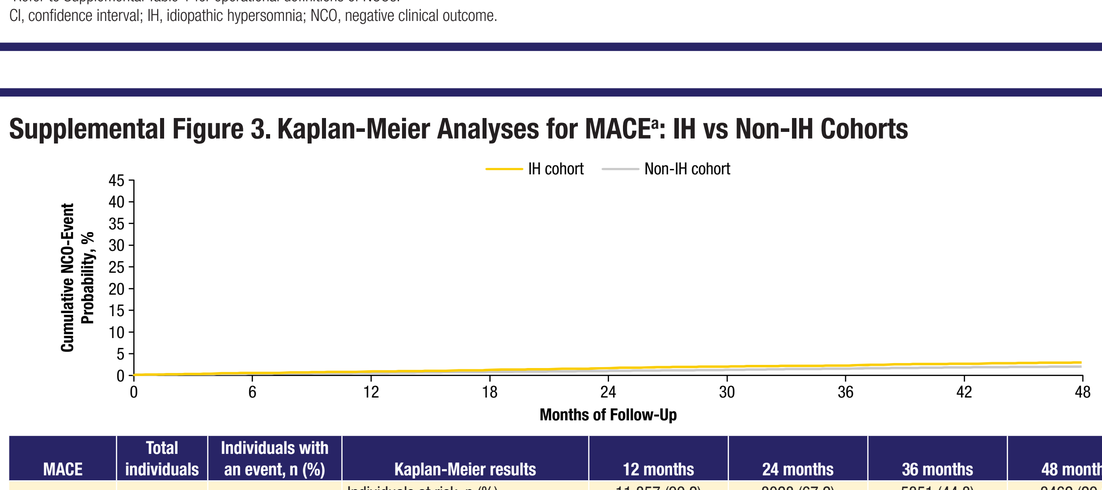
Supplemental Figure 2. Kaplan-Meier Analyses for Hypertension[a]: IH vs Non-IH Cohorts



Hypertension	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,951**	**3061 (25.6)**	Individuals at risk, n (%)	10,571 (88.5)	6605 (55.3)	4080 (34.1)	2485 (20.8)
			Cumulative number of events, n (%)	1380 (11.5)	2171 (18.2)	2619 (21.9)	2864 (24.0)
			Cumulative probability, % (95% CI)	11.5 (11.0, 12.1)	19.4 (18.7, 20.2)	25.9 (25.1, 26.9)	31.3 (30.2, 32.3)
Non-IH cohort	**59,755**	**9752 (16.3)**	Individuals at risk, n (%)	55,951 (93.6)	37,813 (63.3)	22,592 (37.8)	12,904 (21.6)
			Cumulative number of events, n (%)	3804 (6.4)	6487 (10.9)	8078 (13.5)	8935 (15.0)
			Cumulative probability, % (95% CI)	6.4 (6.1, 6.6)	11.6 (11.2, 11.9)	16.1 (15.7, 16.5)	20.2 (19.7, 20.7)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

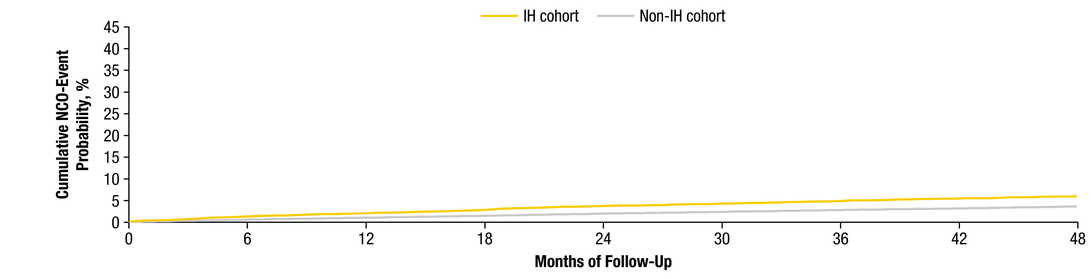
Supplemental Figure 3. Kaplan-Meier Analyses for MACE[a]: IH vs Non-IH Cohorts



MACE	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,951**	**268 (2.2)**	Individuals at risk, n (%)	11,857 (99.2)	8028 (67.2)	5351 (44.8)	3462 (29.0)
			Cumulative number of events, n (%)	94 (0.8)	169 (1.4)	212 (1.8)	246 (2.1)
			Cumulative probability, % (95% CI)	0.8 (0.6, 1.0)	1.5 (1.3, 1.8)	2.1 (1.9, 2.5)	2.9 (2.5, 3.3)
Non-IH cohort	**59,755**	**899 (1.5)**	Individuals at risk, n (%)	59,486 (99.6)	42,431 (71.0)	26,533 (44.4)	15,793 (26.4)
			Cumulative number of events, n (%)	269 (0.4)	510 (0.9)	696 (1.2)	803 (1.3)
			Cumulative probability, % (95% CI)	0.4 (0.4, 0.5)	0.9 (0.8, 1.0)	1.4 (1.3, 1.6)	1.9 (1.8, 2.1)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; MACE, major adverse cardiovascular event; NCO, negative clinical outcome

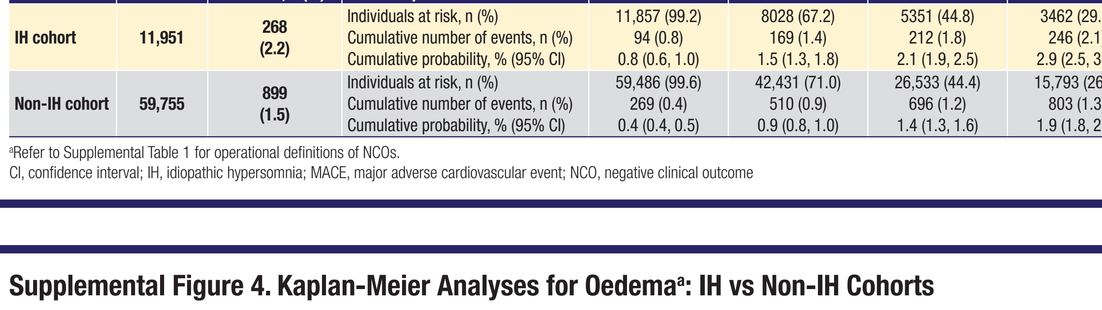
Supplemental Figure 4. Kaplan-Meier Analyses for Oedema[a]: IH vs Non-IH Cohorts



Oedema	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,927**	**568 (4.8)**	Individuals at risk, n (%)	11,690 (98.0)	7828 (65.6)	5184 (43.5)	3327 (27.9)
			Cumulative number of events, n (%)	237 (2.0)	402 (3.4)	478 (4.0)	527 (4.4)
			Cumulative probability, % (95% CI)	2.0 (1.8, 2.3)	3.7 (3.3, 4.0)	4.8 (4.4, 5.2)	5.9 (5.4, 6.4)
Non-IH cohort	**59,722**	**1652 (2.8)**	Individuals at risk, n (%)	59,159 (99.1)	41,976 (70.3)	26,152 (43.8)	15,491 (25.9)
			Cumulative number of events, n (%)	563 (0.9)	1048 (1.8)	1336 (2.2)	1504 (2.5)
			Cumulative probability, % (95% CI)	0.9 (0.9, 1.0)	1.9 (1.8, 2.0)	2.7 (2.5, 2.9)	3.5 (3.3, 3.8)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

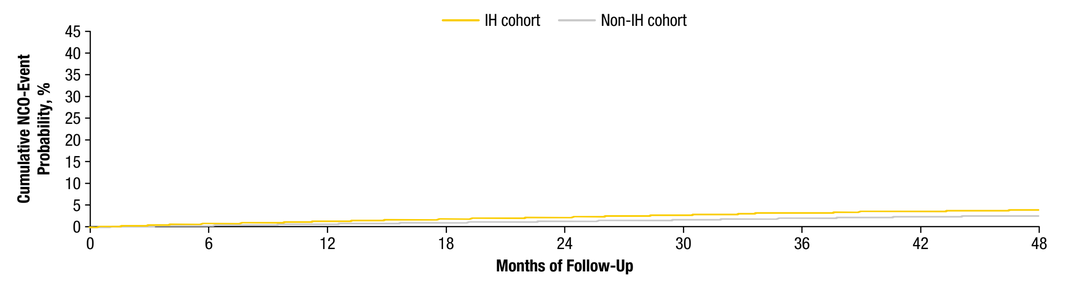
Supplemental Figure 5. Kaplan-Meier Analyses for ≥1 Renal NCO[a]: IH vs Non-IH Cohorts



≥1 renal NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,951**	**552 (4.6)**	Individuals at risk, n (%)	11,691 (97.8)	7864 (65.8)	5185 (43.4)	3348 (28.0)
			Cumulative number of events, n (%)	260 (2.2)	391 (3.3)	474 (4.0)	513 (4.3)
			Cumulative probability, % (95% CI)	2.2 (1.9, 2.5)	3.5 (3.2, 3.8)	4.7 (4.3, 5.1)	5.6 (5.1, 6.1)
Non-IH cohort	**59,755**	**1956 (3.3)**	Individuals at risk, n (%)	58,858 (98.5)	41,730 (69.8)	25,987 (43.5)	15,414 (25.8)
			Cumulative number of events, n (%)	897 (1.5)	1373 (2.3)	1660 (2.8)	1825 (3.1)
			Cumulative probability, % (95% CI)	1.5 (1.4, 1.6)	2.4 (2.3, 2.6)	3.3 (3.1, 3.5)	4.0 (3.8, 4.3)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

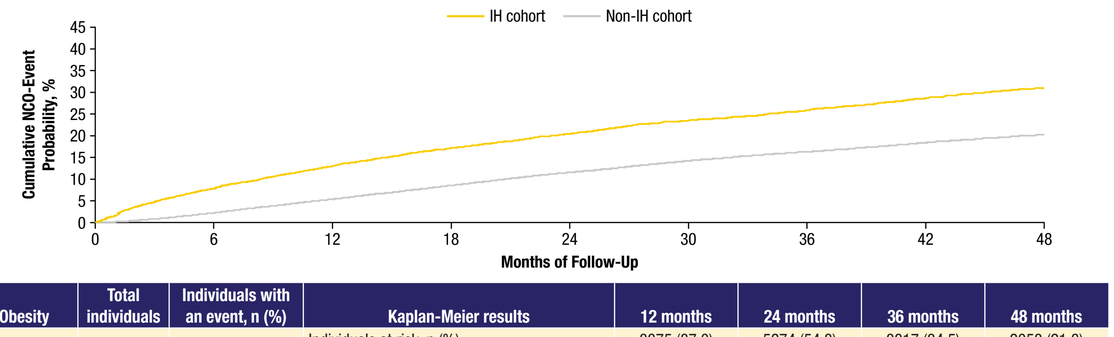
Supplemental Figure 6. Kaplan-Meier Analyses for CV Composite NCO[a]: IH vs Non-IH Cohorts



CV composite NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,951**	**391 (3.3)**	Individuals at risk, n (%)	11,788 (98.6)	7974 (66.7)	5295 (44.3)	3421 (28.6)
			Cumulative number of events, n (%)	163 (1.4)	253 (2.1)	322 (2.7)	358 (3.0)
			Cumulative NCO-event probability, % (95% CI)	1.4 (1.2, 1.6)	2.3 (2.0, 2.5)	3.2 (2.9, 3.6)	4.1 (3.6, 4.5)
Non-IH cohort	**59,755**	**1250 (2.1)**	Individuals at risk, n (%)	59,322 (99.3)	42,233 (70.7)	26,364 (44.1)	15,676 (26.2)
			Cumulative number of events, n (%)	433 (0.7)	765 (1.3)	1001 (1.7)	1130 (1.9)
			Cumulative NCO-event probability (%) (95% CI)	0.7 (0.6, 0.8)	1.4 (1.2, 1.5)	2.0 (1.9, 2.2)	2.6 (2.4, 2.8)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; CV, cardiovascular; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

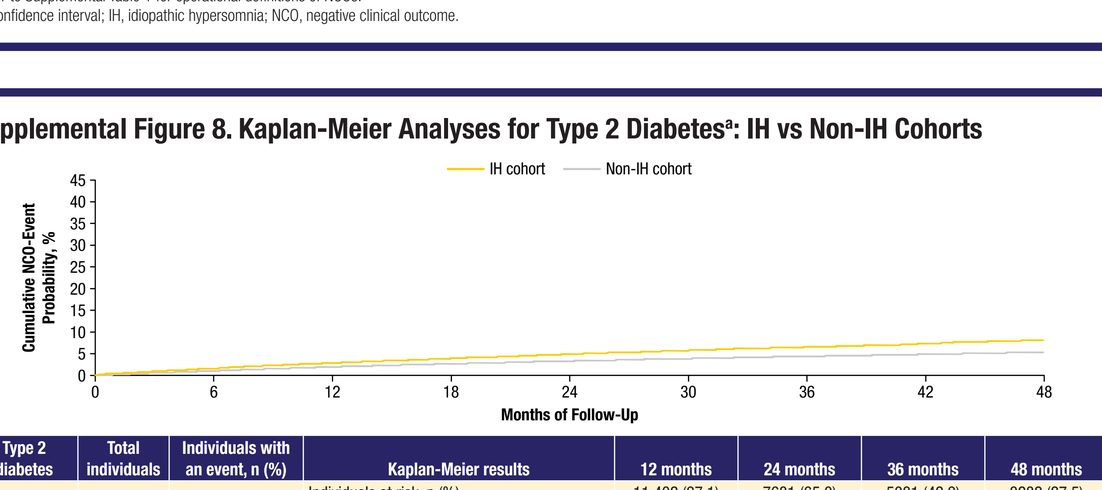
Supplemental Figure 7. Kaplan-Meier Analyses for Obesity[a]: IH vs Non-IH Cohorts



Obesity	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**9626**	**2521 (26.2)**	Individuals at risk, n (%)	8375 (87.0)	5274 (54.8)	3317 (34.5)	2053 (21.3)
			Cumulative number of events, n (%)	1251 (13.0)	1864 (19.4)	2167 (22.5)	2357 (24.5)
			Cumulative NCO-event probability, % (95% CI)	13.0 (12.3, 13.7)	20.5 (19.7, 21.4)	25.9 (25.0, 26.9)	31.0 (29.9, 32.2)
Non-IH cohort	**54,573**	**8904 (16.2)**	Individuals at risk, n (%)	51,640 (94.6)	34,781 (63.7)	20,766 (38.1)	11,786 (21.6)
			Cumulative number of events, n (%)	2934 (5.4)	5861 (10.7)	7416 (13.6)	8189 (15.0)
			Cumulative NCO-event probability (%) (95% CI)	5.4 (5.1, 5.6)	11.5 (11.2, 11.9)	16.3 (15.9, 16.7)	20.3 (19.7, 20.8)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

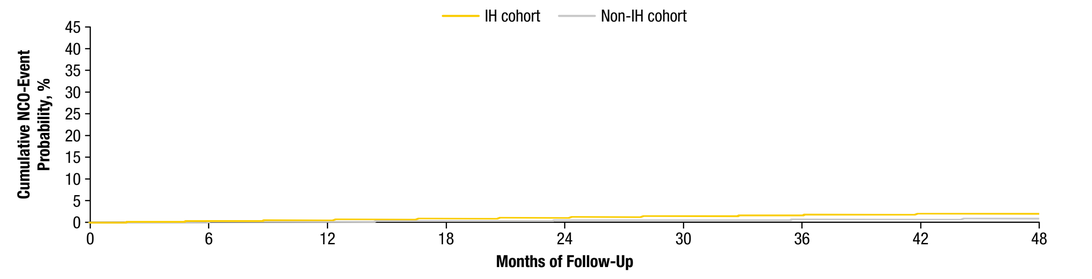
Supplemental Figure 8. Kaplan-Meier Analyses for Type 2 Diabetes[a]: IH vs Non-IH Cohorts



Type 2 diabetes	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,739**	**781 (6.7)**	Individuals at risk, n (%)	11,402 (97.1)	7631 (65.0)	5031 (42.9)	3232 (27.5)
			Cumulative number of events, n (%)	337 (2.9)	536 (4.6)	646 (5.5)	714 (6.1)
			Cumulative NCO-event probability, % (95% CI)	2.9 (2.6, 3.2)	4.9 (4.5, 5.3)	6.5 (6.0, 7.1)	8.1 (7.5, 8.7)
Non-IH cohort	**58,967**	**2618 (4.5)**	Individuals at risk, n (%)	57,812 (98.0)	40,793 (69.2)	25,366 (43.0)	14,989 (25.4)
			Cumulative number of events, n (%)	1154 (2.0)	1852 (3.1)	2217 (3.8)	2418 (4.1)
			Cumulative NCO-event probability (%) (95% CI)	2.0 (1.8, 2.1)	3.3 (3.1, 3.5)	4.4 (4.1, 4.6)	5.3 (5.1, 5.6)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

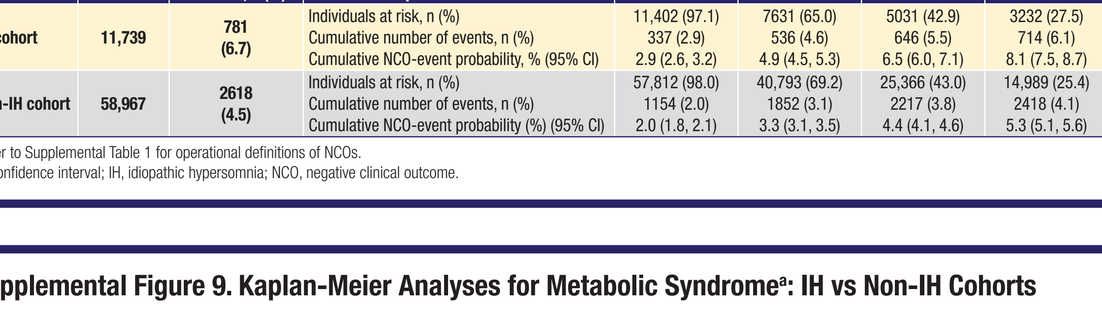
Supplemental Figure 9. Kaplan-Meier Analyses for Metabolic Syndrome[a]: IH vs Non-IH Cohorts



Metabolic syndrome	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**11,842**	**199 (1.7)**	Individuals at risk, n (%)	11,773 (99.4)	7995 (67.5)	5323 (45.0)	3451 (29.1)
			Cumulative number of events, n (%)	69 (0.6)	126 (1.1)	164 (1.4)	179 (1.5)
			Cumulative NCO-event probability, % (95% CI)	0.6 (0.5, 0.7)	1.2 (1.0, 1.4)	1.7 (1.5, 2.0)	2.1 (1.8, 2.4)
Non-IH cohort	**59,575**	**413 (0.7)**	Individuals at risk, n (%)	59,453 (99.8)	42,502 (71.3)	26,642 (44.7)	15,873 (26.6)
			Cumulative number of events, n (%)	122 (0.2)	244 (0.4)	315 (0.5)	359 (0.6)
			Cumulative NCO-event probability (%) (95% CI)	0.2 (0.2, 0.3)	0.4 (0.4, 0.5)	0.6 (0.6, 0.7)	0.9 (0.7, 1.0)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

Supplemental Figure 10. Kaplan-Meier Analyses for Sleep Apnoea[a]: IH vs Non-IH Cohorts



Sleep apnoea	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
IH cohort	**8181**	**2991 (36.6)**	Individuals at risk, n (%)	5669 (69.3)	3610 (44.1)	2343 (28.6)	1472 (18.0)
			Cumulative number of events, n (%)	2512 (30.7)	2761 (33.7)	2870 (35.1)	2928 (35.8)
			Cumulative NCO-event probability, % (95% CI)	30.7 (29.7, 31.7)	34.3 (33.3, 35.4)	36.7 (35.6, 37.8)	38.5 (37.4, 39.7)
Non-IH cohort	**57,690**	**2691 (4.7)**	Individuals at risk, n (%)	56,799 (98.5)	40,090 (69.5)	24,871 (43.1)	14,621 (25.3)
			Cumulative number of events, n (%)	892 (1.5)	1700 (2.9)	2149 (3.7)	2431 (4.2)
			Cumulative NCO-event probability (%) (95% CI)	1.5 (1.4, 1.7)	3.2 (3.0, 3.3)	4.5 (4.3, 4.7)	5.9 (5.6, 6.2)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

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Risk of Sodium-Associated Negative Clinical Outcomes in Individuals With Idiopathic Hypersomnia in the United States: A Real-World Analysis

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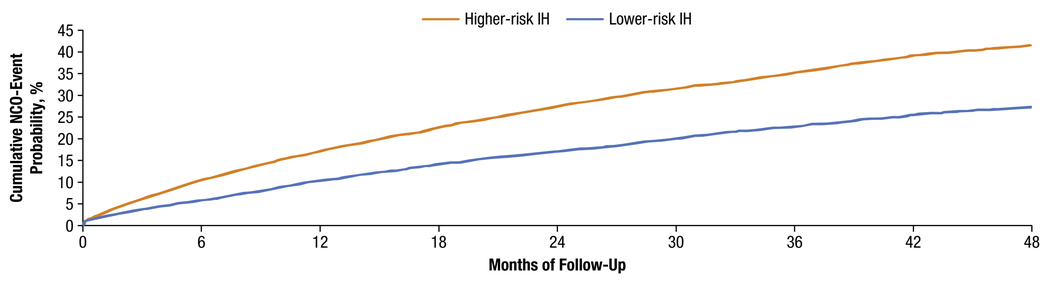
Supplemental Materials

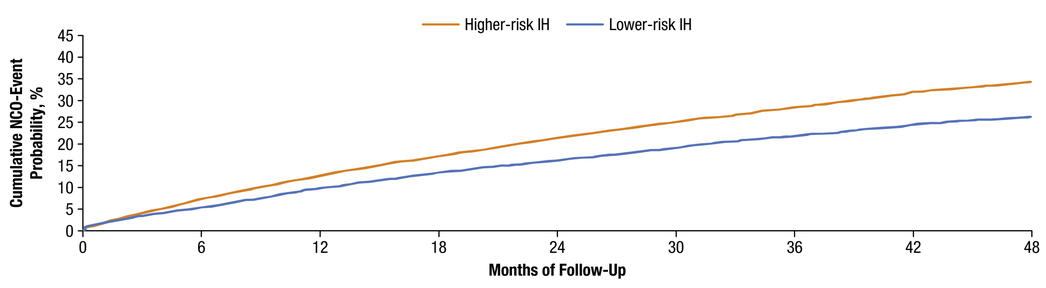
Supplemental Figure 11. Kaplan-Meier Analyses for ≥1 NCO[a]: Risk Subgroups Within IH Cohort



≥1 NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7542	2582 (34.2)	Individuals at risk, n (%)	6258 (83.0)	3705 (49.1)	2208 (29.3)	1322 (17.5)
			Cumulative number of events, n (%)	1284 (17.0)	1934 (25.6)	2264 (30.0)	2444 (32.4)
			Cumulative probability, % (95% CI)	17.0 (16.2, 17.9)	27.4 (26.3, 28.4)	35.1 (33.9, 36.4)	41.4 (40.0, 42.8)
Lower-risk	4409	1004 (22.8)	Individuals at risk, n (%)	3959 (89.8)	2549 (57.8)	1615 (36.6)	989 (22.4)
			Cumulative number of events, n (%)	450 (10.2)	702 (15.9)	851 (19.3)	931 (21.1)
			Cumulative probability, % (95% CI)	10.2 (9.3, 11.1)	16.9 (15.8, 18.1)	22.6 (21.3, 24.1)	27.2 (25.6, 28.9)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

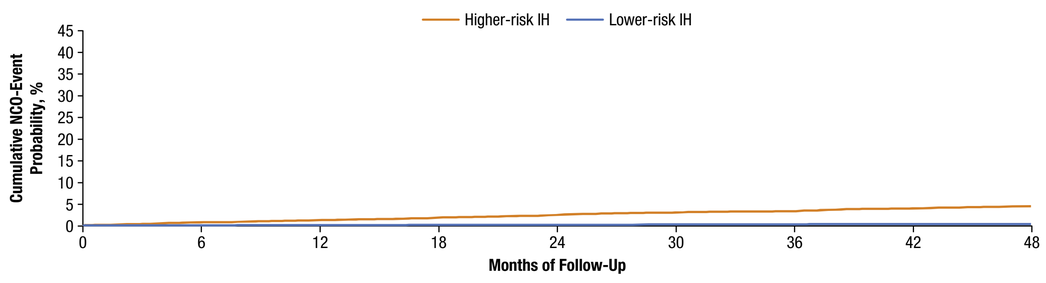
Supplemental Figure 12. Kaplan-Meier Analyses for Hypertension[a]: Risk Subgroups Within IH Cohort



Hypertension	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7542	2100 (27.8)	Individuals at risk, n (%)	6592 (87.4)	4029 (53.4)	2441 (32.4)	1483 (19.7)
			Cumulative number of events, n (%)	950 (12.6)	1501 (19.9)	1803 (23.9)	1970 (26.1)
			Cumulative probability, % (95% CI)	12.6 (11.9, 13.4)	21.3 (20.4, 22.3)	28.4 (27.3, 29.6)	34.3 (32.9, 35.7)
Lower-risk	4409	961 (21.8)	Individuals at risk, n (%)	3979 (90.2)	2576 (58.4)	1639 (37.2)	1002 (22.7)
			Cumulative number of events, n (%)	430 (9.8)	670 (15.2)	816 (18.5)	894 (20.3)
			Cumulative probability, % (95% CI)	9.8 (8.9, 10.7)	16.1 (15.0, 17.3)	21.8 (20.4, 23.2)	26.2 (24.6, 27.9)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

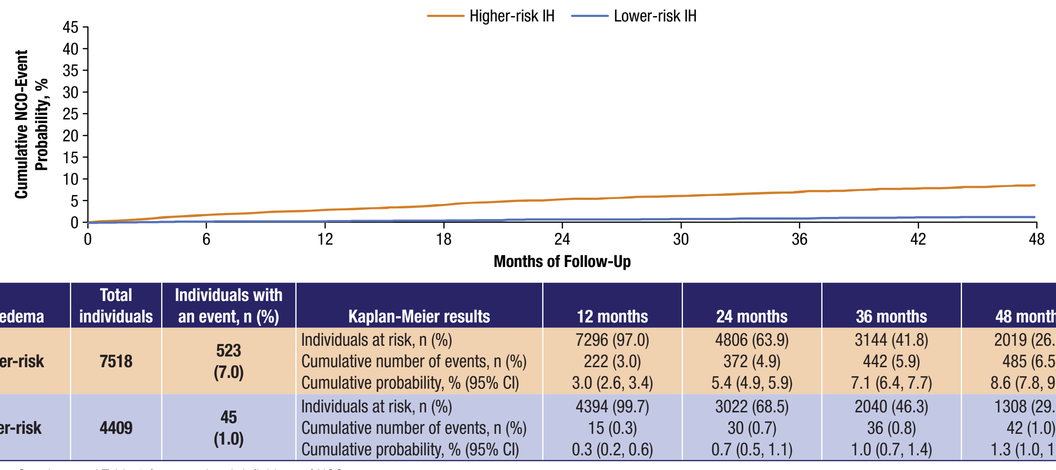
Supplemental Figure 13. Kaplan-Meier Analyses for MACE[a]: Risk Subgroups Within IH Cohort



MACE	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7542	258 (3.4)	Individuals at risk, n (%)	7451 (98.8)	4988 (66.1)	3291 (43.6)	2135 (28.3)
			Cumulative number of events, n (%)	91 (1.2)	164 (2.2)	204 (2.7)	237 (3.1)
			Cumulative probability, % (95% CI)	1.2 (1.0, 1.5)	2.4 (2.0, 2.8)	3.3 (2.9, 3.8)	4.4 (3.9, 5.1)
Lower-risk	4409	10 (0.2)	Individuals at risk, n (%)	4406 (99.9)	3040 (68.9)	2060 (46.7)	1327 (30.1)
			Cumulative number of events, n (%)	3 (0.1)	5 (0.1)	8 (0.2)	9 (0.2)
			Cumulative probability, % (95% CI)	0.1 (0.0, 0.2)	0.1 (0.1, 0.3)	0.2 (0.1, 0.5)	0.3 (0.1, 0.6)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; MACE, major adverse cardiovascular event; NCO, negative clinical outcome.

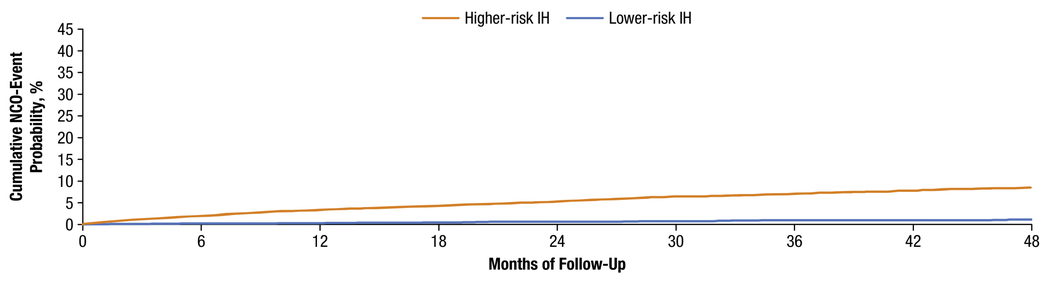
Supplemental Figure 14. Kaplan-Meier Analyses for Oedema[a]: Risk Subgroups Within IH Cohort



Oedema	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7518	523 (7.0)	Individuals at risk, n (%)	7296 (97.0)	4806 (63.9)	3144 (41.8)	2019 (26.9)
			Cumulative number of events, n (%)	222 (3.0)	372 (4.9)	442 (5.9)	485 (6.5)
			Cumulative probability, % (95% CI)	3.0 (2.6, 3.4)	5.4 (4.9, 5.9)	7.1 (6.4, 7.7)	8.6 (7.8, 9.4)
Lower-risk	4409	45 (1.0)	Individuals at risk, n (%)	4394 (99.7)	3022 (68.5)	2040 (46.3)	1308 (29.7)
			Cumulative number of events, n (%)	15 (0.3)	30 (0.7)	36 (0.8)	42 (1.0)
			Cumulative probability, % (95% CI)	0.3 (0.2, 0.6)	0.7 (0.5, 1.1)	1.0 (0.7, 1.4)	1.3 (1.0, 1.8)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

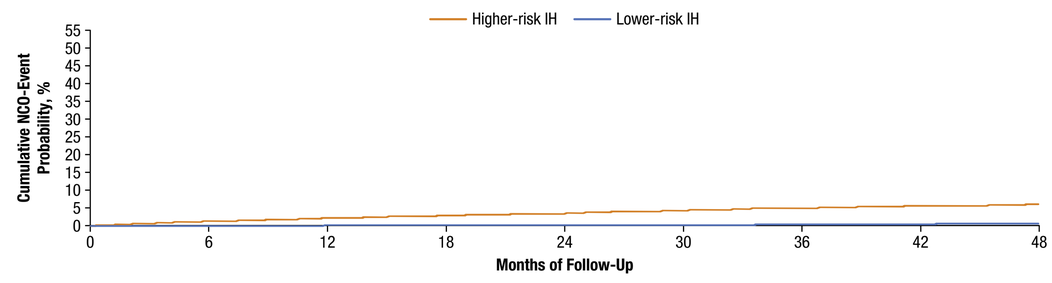
Supplemental Figure 15. Kaplan-Meier Analyses for ≥1 Renal NCO[a]: Risk Subgroups Within IH Cohort



≥1 renal NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7542	505 (6.7)	Individuals at risk, n (%)	7297 (96.8)	4845 (64.2)	3147 (41.7)	2034 (27.0)
			Cumulative number of events, n (%)	245 (3.2)	364 (4.8)	439 (5.8)	476 (6.3)
			Cumulative probability, % (95% CI)	3.2 (2.9, 3.7)	5.1 (4.7, 5.7)	6.9 (6.3, 7.6)	8.2 (7.5, 9.0)
Lower-risk	4409	47 (1.1)	Individuals at risk, n (%)	4394 (99.7)	3019 (68.5)	2038 (46.2)	1314 (29.8)
			Cumulative number of events, n (%)	15 (0.3)	27 (0.6)	35 (0.8)	37 (0.8)
			Cumulative probability, % (95% CI)	0.3 (0.2, 0.6)	0.7 (0.5, 1.0)	1.0 (0.7, 1.4)	1.1 (0.8, 1.6)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

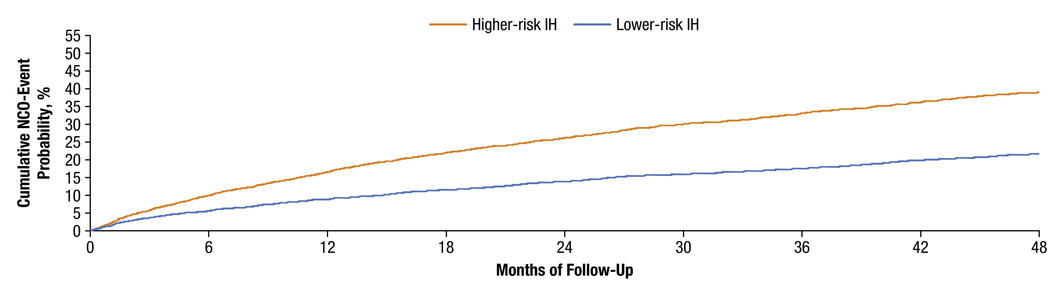
Supplemental Figure 16. Kaplan-Meier Analyses for CV Composite NCO[a]: Risk Subgroups Within IH Cohort



CV composite NCO	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7542	372 (4.9)	Individuals at risk, n (%)	7382 (97.9)	4938 (65.5)	3241 (43.0)	2102 (27.9)
			Cumulative number of events, n (%)	160 (2.1)	245 (3.2)	311 (4.1)	342 (4.5)
			Cumulative NCO-event probability, % (95% CI)	2.1 (1.8, 2.5)	3.5 (3.1, 3.9)	5.0 (4.4, 5.6)	6.1 (5.4, 6.8)
Lower-risk	4409	19 (0.4)	Individuals at risk, n (%)	4406 (99.9)	3036 (68.9)	2054 (46.6)	1319 (29.9)
			Cumulative number of events, n (%)	3 (0.1)	8 (0.2)	11 (0.2)	16 (0.4)
			Cumulative NCO-event probability, % (95% CI)	0.1 (0.0, 0.2)	0.2 (0.1, 0.4)	0.3 (0.2, 0.6)	0.6 (0.4, 1.0)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; CV, cardiovascular; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

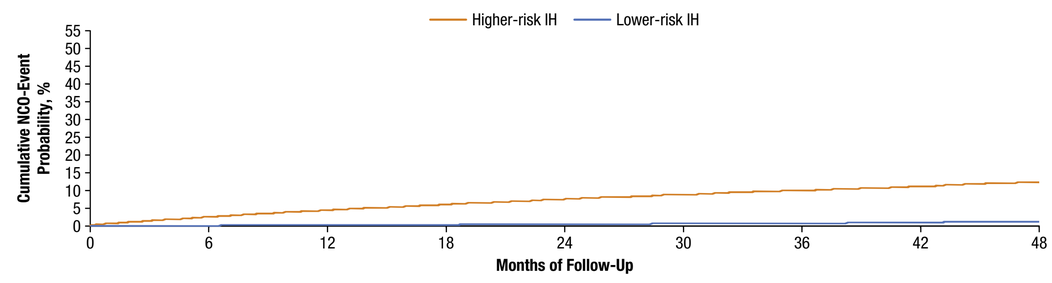
Supplemental Figure 17. Kaplan-Meier Analyses for Obesity[a]: Risk Subgroups Within IH Cohort



Obesity	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	5217	1714 (32.9)	Individuals at risk, n (%)	4355 (83.5)	2656 (50.9)	1611 (30.9)	1004 (19.2)
			Cumulative number of events, n (%)	862 (16.5)	1287 (24.7)	1496 (28.7)	1616 (31.0)
			Cumulative NCO-event probability, % (95% CI)	16.5 (15.5, 17.6)	26.1 (24.9, 27.4)	33.1 (31.7, 34.6)	39.0 (37.4, 40.7)
Lower-risk	4409	807 (18.3)	Individuals at risk, n (%)	4020 (91.2)	2618 (59.4)	1706 (38.7)	1049 (23.8)
			Cumulative number of events, n (%)	389 (8.8)	577 (13.1)	671 (15.2)	741 (16.8)
			Cumulative NCO-event probability, % (95% CI)	8.8 (8.0, 9.7)	13.9 (12.9, 15.0)	17.5 (16.3, 18.8)	21.6 (20.1, 23.2)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

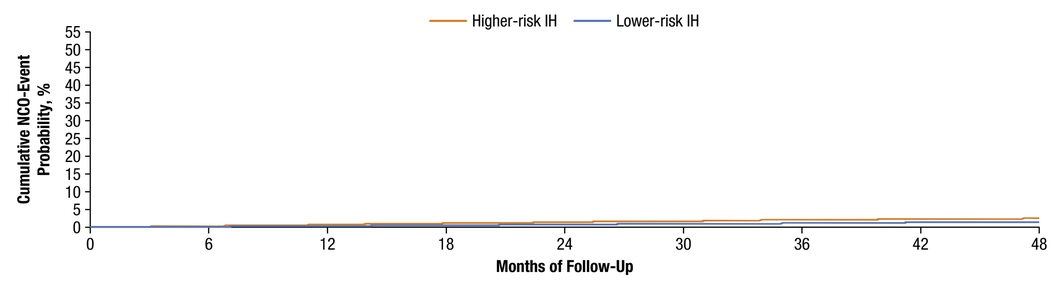
Supplemental Figure 18. Kaplan-Meier Analyses for Type 2 Diabetes[a]: Risk Subgroups Within IH Cohort



Type 2 diabetes	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7330	740 (10.1)	Individuals at risk, n (%)	7005 (95.6)	4603 (62.8)	2984 (40.7)	1916 (26.1)
			Cumulative number of events, n (%)	325 (4.4)	516 (7.0)	618 (8.4)	679 (9.3)
			Cumulative NCO-event probability, % (95% CI)	4.4 (4.0, 4.9)	7.6 (6.9, 8.2)	10.0 (9.3, 10.8)	12.3 (11.3, 13.2)
Lower-risk	4409	41 (0.9)	Individuals at risk, n (%)	4397 (99.7)	3028 (68.7)	2047 (46.4)	1316 (29.8)
			Cumulative number of events, n (%)	12 (0.3)	20 (0.5)	28 (0.6)	35 (0.8)
			Cumulative NCO-event probability, % (95% CI)	0.3 (0.2, 0.5)	0.5 (0.3, 0.8)	0.8 (0.5, 1.2)	1.2 (0.9, 1.7)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

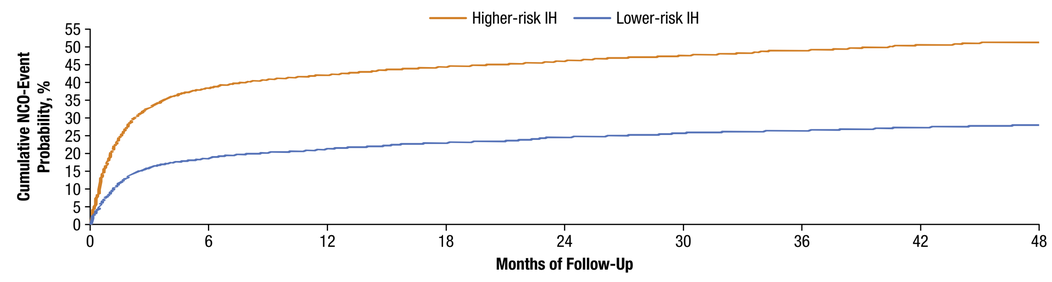
Supplemental Figure 19. Kaplan-Meier Analyses for Metabolic Syndrome[a]: Risk Subgroups Within IH Cohort



Metabolic syndrome	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	7433	149 (2.0)	Individuals at risk, n (%)	7379 (99.3)	4978 (67.0)	3283 (44.2)	2138 (28.8)
			Cumulative number of events, n (%)	54 (0.7)	96 (1.3)	123 (1.7)	134 (1.8)
			Cumulative NCO-event probability, % (95% CI)	0.7 (0.6, 0.9)	1.4 (1.1, 1.7)	2.0 (1.7, 2.4)	2.4 (2.0, 2.9)
Lower-risk	4409	50 (1.1)	Individuals at risk, n (%)	4394 (99.7)	3017 (68.4)	2040 (46.3)	1313 (29.8)
			Cumulative number of events, n (%)	15 (0.3)	30 (0.7)	41 (0.9)	45 (1.0)
			Cumulative NCO-event probability, % (95% CI)	0.3 (0.2, 0.6)	0.8 (0.5, 1.1)	1.2 (0.9, 1.7)	1.5 (1.1, 2.0)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.

Supplemental Figure 20. Kaplan-Meier Analyses for Sleep Apnoea[a]: Risk Subgroups Within IH Cohort



Sleep apnoea	Total individuals	Individuals with an event, n (%)	Kaplan-Meier results	12 months	24 months	36 months	48 months
Higher-risk	3772	1828 (48.5)	Individuals at risk, n (%)	2190 (58.1)	1333 (35.3)	835 (22.1)	516 (13.7)
			Cumulative number of events, n (%)	1582 (41.9)	1706 (45.2)	1768 (46.9)	1800 (47.7)
			Cumulative NCO-event probability, % (95% CI)	41.9 (40.4, 43.5)	45.8 (44.2, 47.5)	48.9 (47.2, 50.6)	51.2 (49.4, 53.0)
Lower-risk	4409	1163 (26.4)	Individuals at risk, n (%)	3479 (78.9)	2277 (51.6)	1508 (34.2)	956 (21.7)
			Cumulative number of events, n (%)	930 (21.1)	1055 (23.9)	1102 (25.0)	1128 (25.6)
			Cumulative NCO-event probability, % (95% CI)	21.1 (19.9, 22.3)	24.5 (23.2, 25.8)	26.3 (25.0, 27.7)	27.8 (26.4, 29.3)

[a]Refer to Supplemental Table 1 for operational definitions of NCOs.
CI, confidence interval; IH, idiopathic hypersomnia; NCO, negative clinical outcome.