East Riding Varenicline PGD Service

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Objectives: PGD refresher: What? When? How?

- Information about the East Riding Stop Smoking Service
- Refresher - the use of varenicline and its place in smoking cessation
- What updates have been made to the East Riding PGD and Why?
- Smoking Cessation Service Improved Outcomes4Health reporting and payments pathway
- Lessons learned from the Stop Smoking varenicline pathway

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What is a PGD?

- A ***written instruction*** for the ***supply or administration*** of a medicine to a group of patients who may ***not be individually identified*** before presentation for treatment.

- Remember: supply of a POM other than on prescription or in accordance with a PGD may be a criminal offence.

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When to use a PGD

- Most patients should be treated on an individual, patient-specific basis.
- "Use PGDs in limited situations where there is an advantage for patient care".
- Patient safety must not be compromised.
- Must be consistent with appropriate professional relationships & accountability.

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How to use a PGD (1)

- Pharmacists must at all times work in line with GPhC Professional Standards.
- PGD must be authorised for use in your organisation.
- **You must sign the PGD**.
- Supply cannot be delegated to anyone else

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How to use a PGD (2)

- No scope in PGD for interpretation, discretion or adjustment.
  - **NOT** prescribing, it is supply/administration.

- A patient **excluded** from treatment under a PGD might still be suitable for treatment, but only on prescription from a doctor or non-medical prescriber if applicable.

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Varenicline (CHAMPIX®)

- VARENICLINE is indicated for smoking cessation in adults.
- Black triangle status is now removed
- MHRA advice (later slide) superseded with results of the EAGLES trial results

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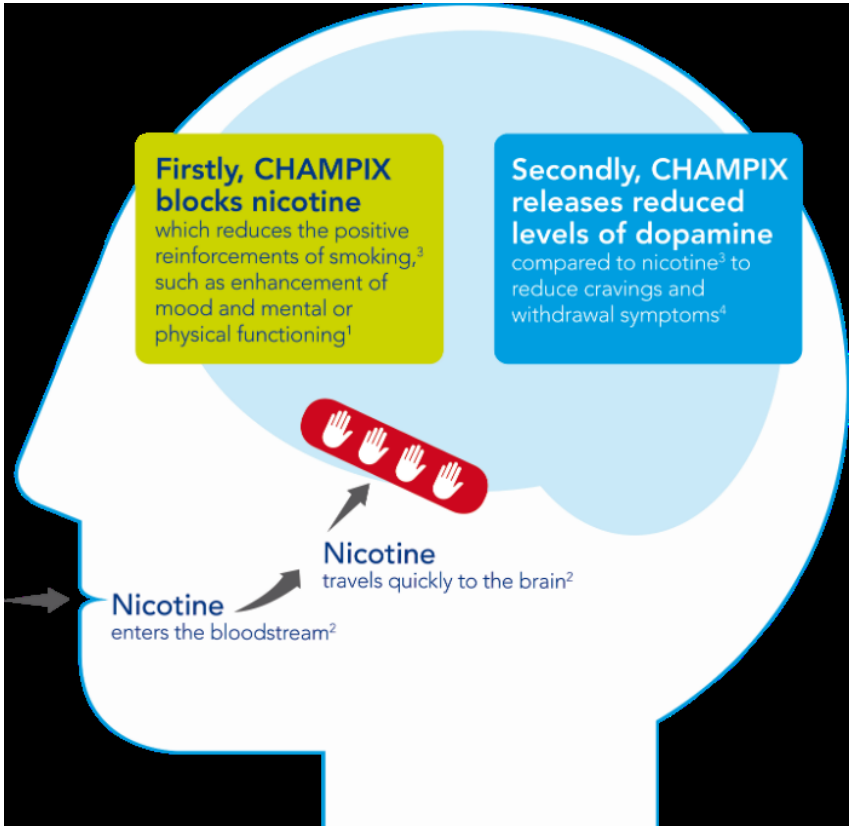
Mode of Action



Inclusion Criteria

- Resident of East Riding of Yorkshire
- Attending behavioural support sessions
- Over 18
- Consented
- Notification via PharmOutcomes
- **Full clinical assessment by pharmacist before supply with no exclusion criteria**

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PGD Exclusion Criteria (1)

- Under 18
- Pregnant/breastfeeding
- Known hypersensitivity to varenicline or excipients
- Renal impairment / renal disease
- Patients with a current pyschiatric illness including schizophrenia, bipolar disorder and/or major depression **(People with a history of psychiatric illness including depression are no longer excluded)**
- History of seizures or conditions which lower seizure threshold

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PGD Exclusion Criteria (2)

- Unstable cardiovascular disease or recent cardiovascular event
- Taking any medication listed below:
  - Clozapine
  - Any other antipsychotic medication
  - Any antidepressant medication (for depression)

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Cautions: CYP1A2 smoking induction

Physiological changes resulting from smoking cessation, with or without treatment with stop smoking products, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary:

- **Theophylline**: discuss with GP within 14 days
- **Warfarin**: arrange earlier/more frequent INR test
- **Insulin**: watch for hypos, test more frequently

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Other drugs affected

- Pharmacokinetic changes as a result of stopping smoking MAY also be important in patients taking:
  - Olanzapine:
  - Methadone:
  - Chlorpromazine
  - Cinacalet
  - Ropinirole

- Patient discuss with GP/Key Worker/Specialist

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Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial.

Robert M Anthenelli, Neal L Benowitz, Robert West, Lisa St Aubin, Thomas McRae, David Lawrence, John Ascher, Cristina Russ, Alok Krishen, A Eden Evins

Lancet 2016 387: 2507-2520

EAGLES = EVALUATING ADVERSE EVENTS IN A GLOBAL SMOKING CESSATION STUDY

Background

- Chantix/Champix (CHX) labelling in some countries, including the US currently includes a boxed warning regarding serious neuropsychiatric (NPS) events
  - The warning is based on post-marketing reports of events that occurred in varenicline patients with and without pre-existing psychiatric disease
  - This boxed warning was included in the Chantix (US) label in 2009.

- Study A3051123 (EAGLES) is a post marketing requirement (PMR) in the US and a post authorization safety study (PASS) in the EU for varenicline.
  - The FDA issued a post-marketing requirement to conduct a randomised controlled trial to assess the risk of serious neuropsychiatric adverse events.
  - The study protocol was developed with input from FDA and EMA. This study, which is also a PMR for bupropion in the US, is sponsored by Pfizer in collaboration with GSK.

Anthenelli RM, et al. Lancet 2016 387: 2507-2520

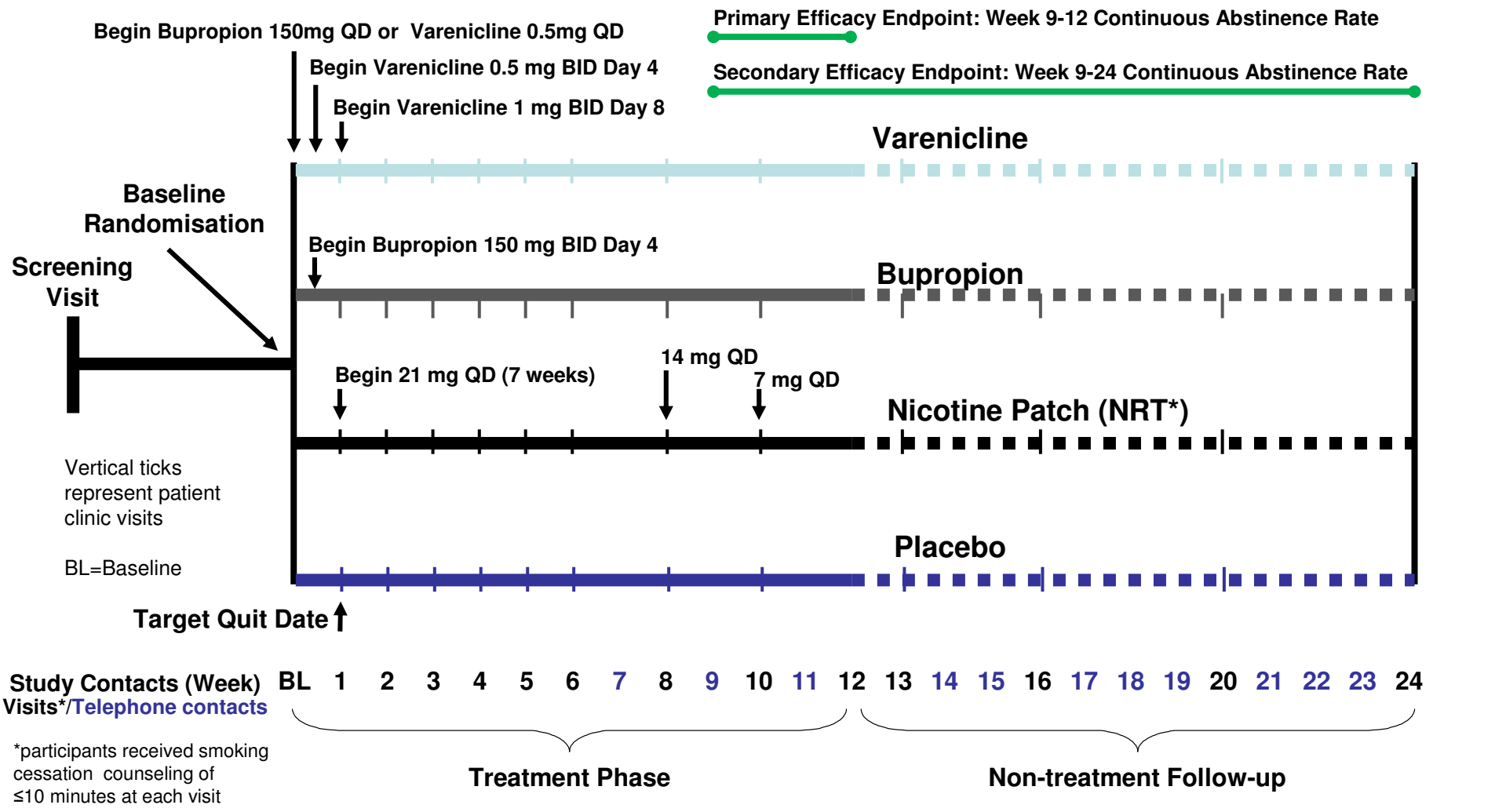
Objectives/Study Design

- **Main Objectives:**
  - **Safety**: Characterise the neuropsychiatric safety profiles of varenicline and bupropion vs. placebo in subjects with and without a diagnosis of psychiatric disorder
  - **Efficacy**: Compare smoking abstinence rates of varenicline and bupropion relative to placebo in subjects with and without a diagnosis of psychiatric disorder
- **Study Design:** Multi-national, randomised, double-blind, placebo-controlled and active-controlled (nicotine patch*) trial of varenicline (1mg BID) and bupropion (150mg BID) for 12 weeks followed by 12 weeks of non-treatment follow up.
  - Randomised 1:1:1:1 to varenicline, bupropion, nicotine patch*, or placebo
  - Primary comparisons: varenicline vs. placebo and bupropion vs. placebo
  - Triple dummy design: all 3 active study drugs were blinded
  - Up to 10 minutes of smoking cessation counseling was provided at each visit
  - Medication compliance was assessed with patch and pill counts at each visit

* NRT Patch (NiQuitin™)

Anthenelli RM, et al. Lancet 2016 387: 2507-2520

EAGLES Study Diagram



Adapted from Anthenelli RM, et al. Lancet 2016 387: 2507-2520 (Suppl)

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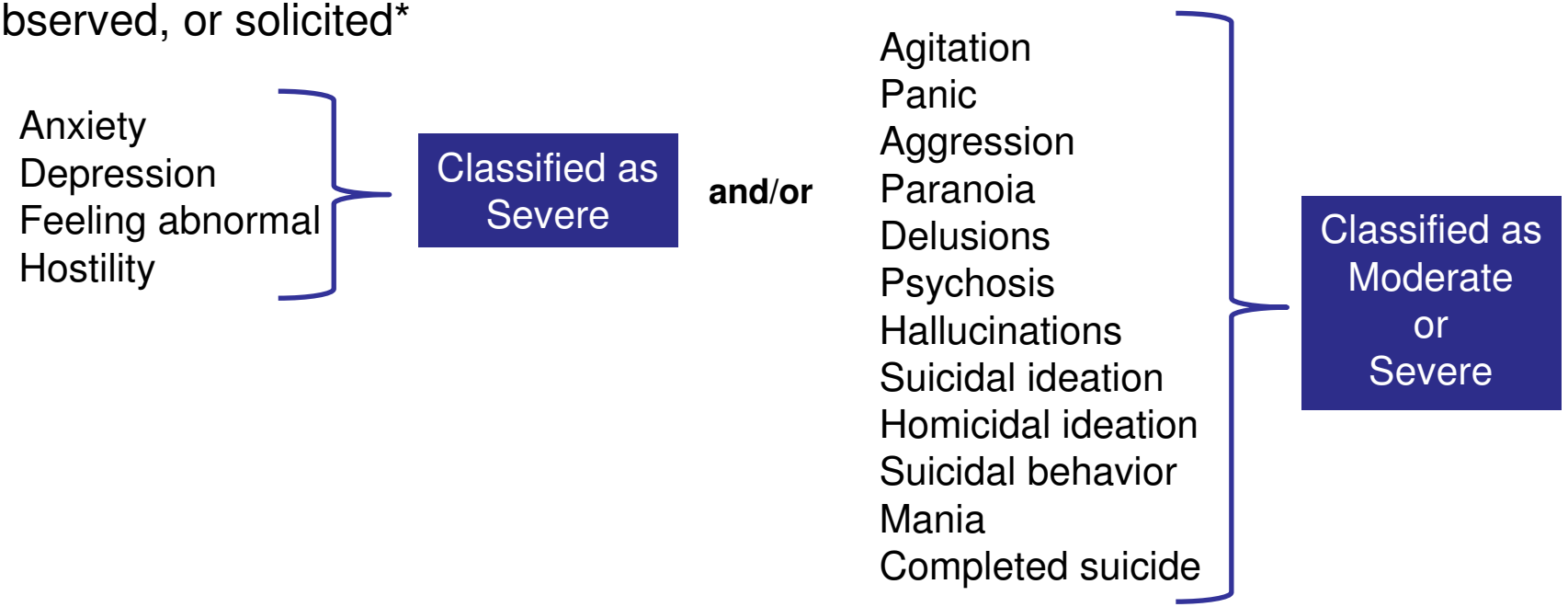
Primary Endpoints

Primary Safety Endpoint: Composite endpoint of the number (%) of subjects reporting at least one of the following Neuropsychiatric (NPS) adverse events (AEs) during treatment and up to 30 days after last dose. Events could be volunteered, observed, or solicited*

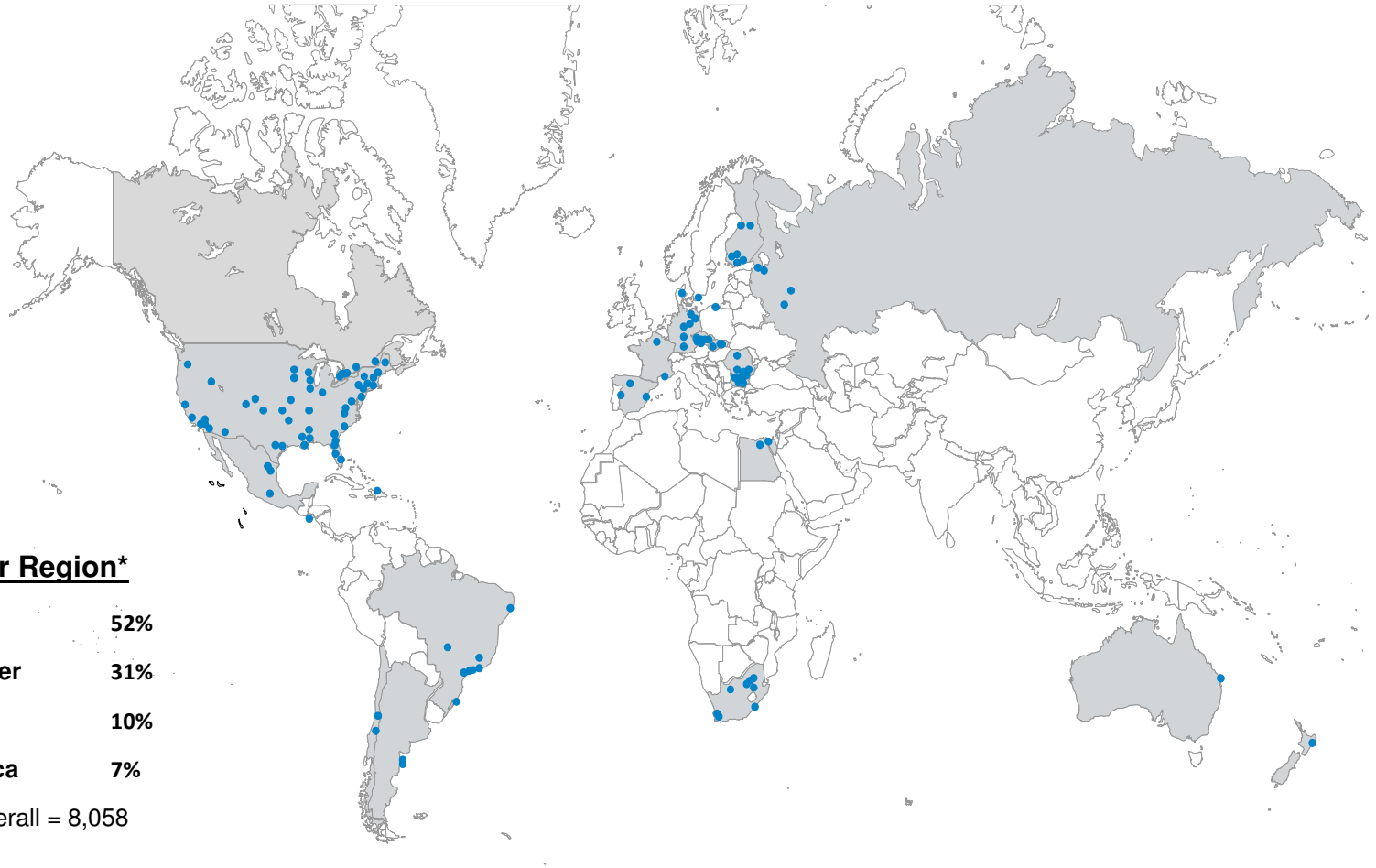


Primary Efficacy Endpoint: CO-confirmed 4-week continuous abstinence rates (CAR) at Weeks 9-12

* Including use of the Neuropsychiatric Adverse Event Interview (NAEI)

Anthenelli RM, et al. Lancet 2016 387: 2507-2520

EAGLES Study Sites: 140 centres in 16 countries on 5 continents



Study Population Per Region*

United States	**52%**
Western Europe and Other	**31%**
Eastern Europe	**10%**
South and Middle America	**7%**

*All treated population; Overall = 8,058

Anthenelli RM, et al. Lancet 2016 387: 2507-2520

Participant Disposition Summary

Screened = 11,186 Enrolled = 8,144	Number (%) of Subjects			
	Varenicline	Bupropion	NRT*	Placebo
Non-Psychiatric Cohort				
All Randomised (ITT)	1005	1001	1013	1009
All Treated (Safety)	990	989	1006	999
Completed Study	787 (79.5%)	783 (79.2%)	767 (76.2%)	787 (78.8%)
Psychiatric Cohort				
All Randomised (ITT)	1032	1033	1025	1026
All Treated (Safety)	1026	1017	1016	1015
Completed Study	811 (79.0%)	803 (79.0%)	790 (77.8%)	765 (75.4%)

ITT: Intent-to-treat population (efficacy analysis).
All Treated population (safety analysis): received at least one dose of study drug

Medication compliance overall was about 80% across the four treatment groups

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Primary Endpoint: Neuropsychiatric AE Composite Endpoint

Cohort	Number (percentage) of subjects with ≥1 events (n/N, %)			
	Varenicline	Bupropion	NRT*	Placebo
Non-Psychiatric	13/990 **1.3%**	22/989 **2.2%**	25/1006 **2.5%**	24/999 **2.4%**
Psychiatric	67/1026 **6.5%**	68/1017 **6.7%**	53/1016* **5.2%**	50/1015 **4.9%**
Overall (both cohorts)	80/2016 **4.0%**	90/2006 **4.5%**	78/2022 **3.9%**	74/2014 **3.7%**

AEs reported during treatment and ≤30 days after last dose.

* One additional participant (Psychiatric/NRT group) who reported moderate suicidal ideation was identified after clinical database lock and was not included in the analysis

Based on the pre-specified statistical model:

- There was an interaction between treatment and cohort. Risk differences between treatments were calculated separately for each cohort

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Secondary Endpoint: Severe-Only NPS AEs in the Primary Endpoint

	Varenicline	Bupropion	NRT*	Placebo
Non-Psychiatric Cohort, N	**990**	**989**	**1006**	**999**
NPS AE Primary Endpoint, n (%)	13 (1.3%)	22 (2.2%)	25 (2.5%)	24 (2.4%)
Severe only	**1 (0.1%)**	**4 (0.4%)**	**3 (0.3%)**	**5 (0.5%)**
Psychiatric Cohort, N	**1026**	**1017**	**1016**	**1015**
NPS AE Primary Endpoint, n (%)	67 (6.5%)	68 (6.7%)	53 (5.2%)	50 (4.9%)
Severe only	**14 (1.4%)**	**14 (1.4%)**	**14 (1.4%)**	**13 (1.3%)**

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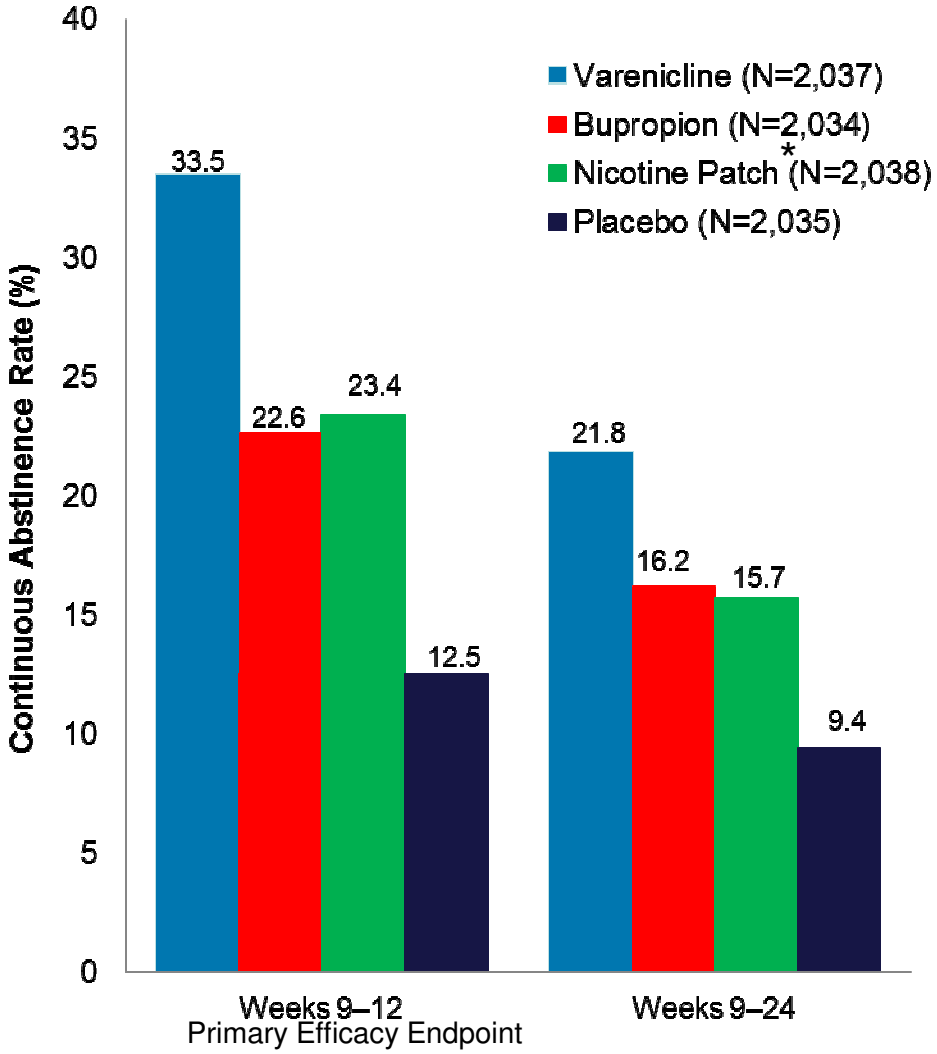
Efficacy: Continuous Abstinence Rates (CARs) All Treated Subjects (Both Cohorts Pooled)



Primary comparisons:
Varenicline vs. placebo
Bupropion vs. placebo

Statistics Summary (both time points):
Varenicline, Bupropion, or Nicotine Patch* vs. placebo (p<0·0001)
Varenicline vs. Bupropion or Nicotine Patch* (p<0·0001)
Bupropion vs. Nicotine Patch* (p=0.6) *NS*

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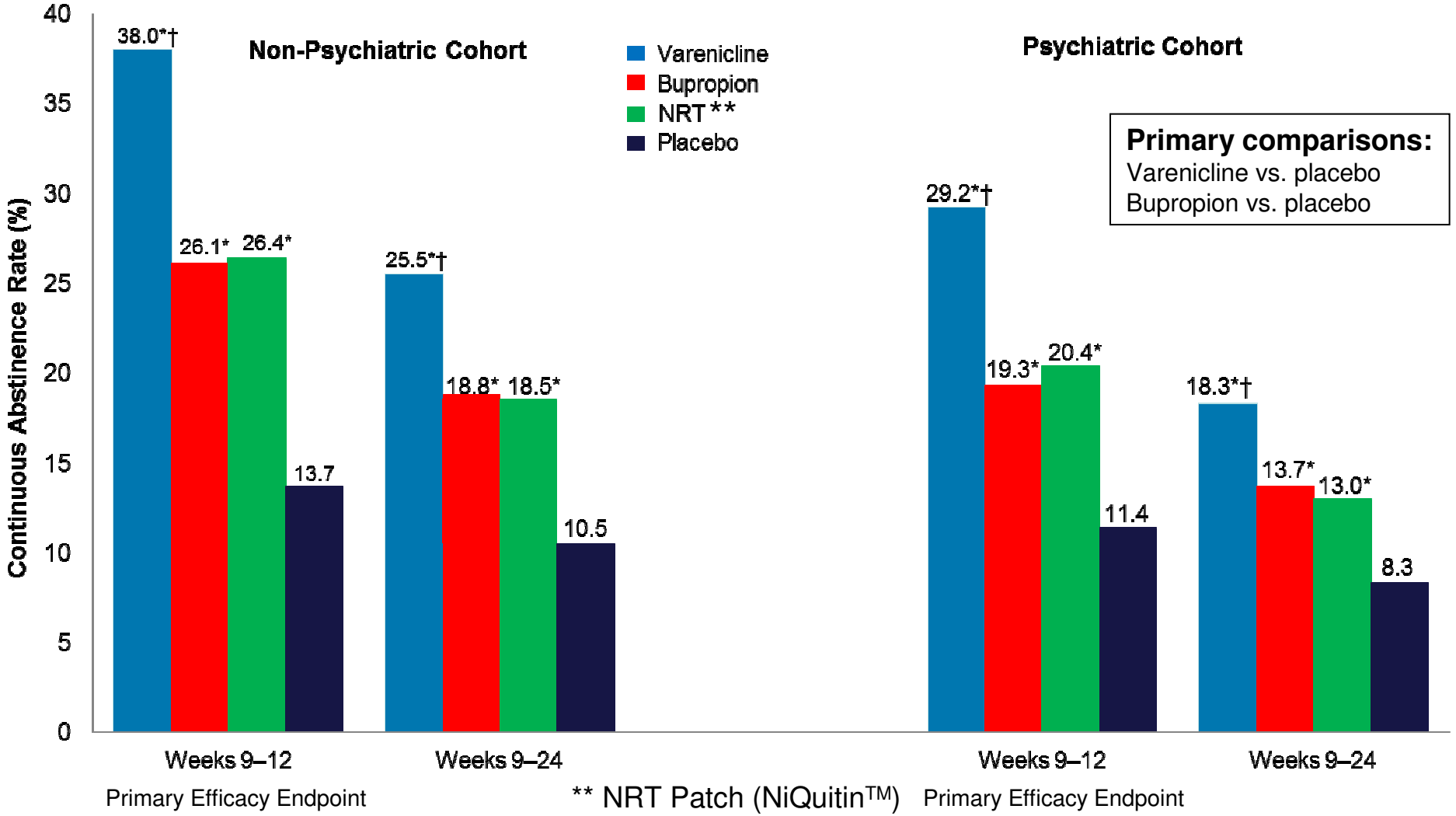
Efficacy: Continuous Abstinence Rates (CARs) Non-Psychiatric and Psychiatric Cohorts



*p=0.0007 or less vs. placebo; †p=0.0047 or less vs Bupropion or Nicotine Patch**; Bupropion vs. Nicotine Patch** =NS

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Authors' Key Limitations

- Findings may not generalize to smokers with untreated or unstable psychiatric disease
- The duration of and frequent monitoring during the study might not mirror a real world smoking cessation attempt.
- Low power to detect rare NPS events such as completed suicide
- Light smokers not included

Anthenelli RM, et al. Lancet 2016 387: 2507-2520

Authors' Conclusions

- Safety
  - This study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch* or placebo.

- Efficacy
  - Varenicline was more effective than placebo, nicotine patch*, and bupropion in helping smokers achieve abstinence
  - Bupropion and nicotine patch* were more effective than placebo.

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Awareness for People with A History of Psychiatric Illness

- Monitor closely and advise accordingly
- Watch for possible emergence of significant depressive symptoms
- Advise patients affected to discontinue treatment and seek prompt medical advice if they develop:
  - Agitation
  - Depressed Mood of Concern
  - Suicidal Thoughts

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Dose

- The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

- **Days 1 – 3:**

0.5 mg once daily

- **Days 4 – 7:**

0.5 mg twice daily

- **Day 8 – End of treatment**

1mg twice daily

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Treatment

- Prior to first visit the patient should set a quit date. VARENICLINE dosing should usually start at 1-2 weeks before this date.
- Patients who report they cannot tolerate adverse reactions of VARENICLINE may have the dose lowered temporarily or permanently to 0.5 mg twice daily.
- Patients can be treated with VARENICLINE for up to 14 weeks under PGD.

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What to expect when stopping smoking with VARENICLINE

- The most common adverse events with VARENICLINE
- Nausea 32%
- Insomnia 19.1%
- Headache 17.7%
- Abnormal dreams 13.8%
- Nasopharyngitis 10.7%

Please refer to the Summary of Product Characteristics for further information about adverse events that have been reported during/after Champix therapy

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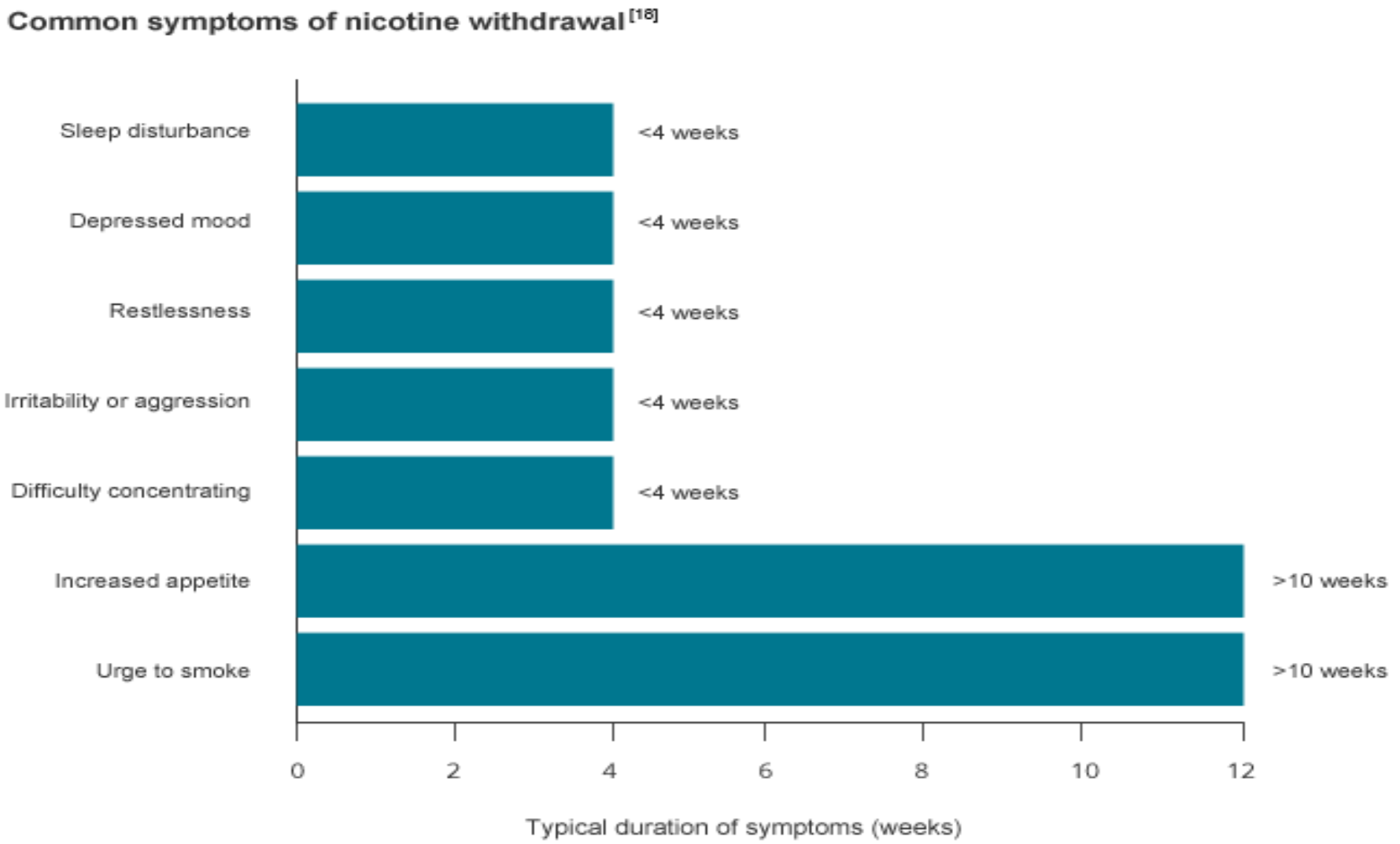
Nicotine Withdrawal



Cardiovascular events

- Certain cardiovascular events were reported more frequently in patients treated with VARENICLINE.

- Patients taking VARENICLINE should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke.

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Reporting adverse reactions

- Monitor concordance and adverse reactions at follow-up.
- Report **all** adverse reactions in accordance with the UK Adverse Drug Reaction Reporting Guidelines (Yellow card system available at; http://www.yellowcard.gov.uk/).
- Clients who report agitation/ depression/ suicide ideation /change of mood or new or worsening cardiovascular symptoms must stop treatment immediately and seek prompt medical advice.

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Resources 1: Declaration of Competence

- CPPE – PGD e-learning program
- Consultation skills training
- Knowledge of the Summary of Product Characteristics (SPC) for Varenicline▼
- Knowledge and understanding of the East Riding of Yorkshire Varenicline▼ Patient group direction
- Knowledge and understanding of the East Riding of Yorkshire Varenicline▼ Service specification
- Attendance at the Varenicline ▼Service launch event or liaison with someone who has attended the launch event.

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Resources 2: Declaration of Competence

- NICE Patient Group Directions: Medicines Practice Guidance: August 2013 link
- NICE Stop smoking services guidelines (PH10): February 2008 link
- NICE Varenicline for smoking cessation Technology Appraisal guidance (TA123): July 2007 link

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Additional Local Resources

- Pharmacist Information Sheet
- Process Map
- Health Trainer Client Referral Pre-screen Checklist for referral
- Pharmacist Client Assessment Form
- Information Leaflet provided to the client with the supply

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Questions or Comments?

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