

# Respiratory Research Review™

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Issue 142 – 2017

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### Abbreviations used in this issue

**BCOS** = bronchiectasis-COPD overlap syndrome  
**BROS** = bronchiectasis-rheumatoid arthritis overlap syndrome  
**BSI** = Bronchiectasis Severity Index  
**CF** = cystic fibrosis  
**CFTR** = cystic fibrosis transmembrane conductance regulator  
**COPD** = chronic obstructive pulmonary disease  
**FEV** = forced expiratory volume  
**QOL** = quality of life

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## Welcome to this November issue of Respiratory Research Review with the focus on bronchiectasis and CF (cystic fibrosis).

Bronchiectasis may be close to the tipping point of losing its orphan status – probably a function of the increasing incidence, great clinical research and up-to-date practical guidelines. Approximations of the current incidence are around 500 per 100,000 people. Bronchiectasis is commonly found in patients with a diagnosis of asthma and COPD; it is estimated that about 1 in 20 patients with COPD also have bronchiectasis. Bronchiectasis also coexists with HIV infection, rheumatoid arthritis, inflammatory bowel disease and pulmonary fibrosis.

'Raising awareness of bronchiectasis in primary care: overview of diagnosis and management strategies in adults' is a [review article](#) covering the most common causes of bronchiectasis, the goals of treatment and treatment algorithms. The case-based discussions on how to diagnose bronchiectasis in primary care are particularly helpful. The authors suggest that one should suspect bronchiectasis in patients with severe, persistent, unusual or recurrent (acronym: SPUR) respiratory tract infections. Most cases of bronchiectasis can be managed in primary care, and the authors give some guidance on radiological examinations, spirometry, twice yearly sputum surveillance and indicators of when to refer to secondary care. In Respiratory Research Review, [issue 106](#), we reviewed the BSI (Bronchiectasis Severity Index) and the FACED (FEV<sub>1</sub>, age, *Pseudomonas* colonisation, more than two lobes involved based on radiology); the second score is the best long-term predictor of outcome (Respiratory Research Review, [issue 130](#)).

While the aforementioned review covered essential areas of bronchiectasis in seven pages including diagrams and tables, the updated [European Respiratory Society guidelines](#) on the management of adult bronchiectasis occupies 23 pages. Still, by using the style of focussing on key clinical questions, they are surprisingly readable. I urge the reader to glance at either of these free-to-view documents; here are only the headline key clinical questions:

- Is standardised testing for the cause of bronchiectasis beneficial when compared with no standardised testing? (yes)
- Are courses of 14–21 days of systemic antibiotic therapy compared with short courses (≤14 days) beneficial for treating adult bronchiectasis patients with an acute exacerbation? (yes)
- Is eradication treatment beneficial for treating bronchiectasis patients with a new isolate of potentially pathogenic micro-organisms in comparison with no eradication treatment? (yes)
- Should long-term anti-inflammatory agents like inhaled corticosteroids be used in adult patients with bronchiectasis? (no)
- Is long-term antibiotic treatment (>3 months) compared with no treatment beneficial for treating adult bronchiectasis patients? (probably yes)
- Is long-term mucocactive treatment (>3 months) compared with no treatment beneficial for treating adult bronchiectasis patients? (probably yes)
- Is long-term bronchodilator treatment (>3 months) compared with no treatment beneficial for adult bronchiectasis patients? (no)
- Are surgical interventions more beneficial compared with standard (nonsurgical) treatment for adult bronchiectasis patients? (no)
- Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than control (no physiotherapy treatment) in adult bronchiectasis patients? (yes)

The world of CF is changing rapidly, and I am proud that many of my nursing colleagues have been acknowledged for their complex, crucial and competent work (Kai Tiaki Nursing New Zealand 2017;23[5]:14–28). New treatments and treatment combinations addressing some of the underlying pathophysiology are entering clinical care, and when the 'first-in-human' lentivirus [trial](#) in patients with CF is positive, we may have a viral vector to deliver the correct gene, about 100-fold more potent than nonviral, liposomal carriers.

We hope you enjoy the selection and, as always, we are looking forward to comments or questions.

Kind regards

Professor Lutz Beckert

[lutzbeckert@researchreview.co.nz](mailto:lutzbeckert@researchreview.co.nz)

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## Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry

**Authors:** Aksamit TR et al.

**Summary:** The characteristics of 1826 adult registry patients with bronchiectasis from the US Bronchiectasis Research Registry were reported. A history of nontuberculous mycobacterial disease or nontuberculous mycobacteria isolated at baseline evaluation was present for 63% of the patients, and such patients were older, were mainly female, had bronchiectasis diagnosed at a more advanced age and had more gastro-oesophageal reflux disease than those without nontuberculous mycobacteria. Patients without nontuberculous mycobacteria had more asthma, primary immunodeficiency and primary ciliary dyskinesia. Evidence of airflow obstruction was seen on spirometry in 51% of patients, and those with nontuberculous mycobacteria were more likely to have diffusely dilated airways and tree-in-bud abnormalities. *Pseudomonas* spp. and *Staphylococcus aureus* were detected more often in patients without nontuberculous mycobacteria. Patients with nontuberculous mycobacteria used bronchial hygiene measures more often, and those without nontuberculous mycobacteria used antibiotics for exacerbations, rotating oral antibiotics, steroids and inhaled bronchodilators more often.

**Comment:** In other illnesses, like interstitial lung disease or pulmonary arterial hypertension, registries provide great insights, assist us to articulate the correct research questions, and act as a reservoir for patients. Here, the US authors offer insights into their registry from 13 US sites, analysing almost 2000 patients. Patients were predominantly female, white nonsmokers with a mean age of 64 years. It was not surprising 63% had co-existing nontuberculous mycobacteria; however, it was surprising that 39% used inhaled steroids despite a lack of evidence to support their use. Also surprising, **the bottom line: despite good evidence, airways clearance techniques were only performed in about half of patients with bronchiectasis.**

**Reference:** *Chest* 2017;151(5):982–92

[Abstract](#)

## The development and validation of the Bronchiectasis Health Questionnaire

**Authors:** Spinou A et al.

**Summary:** Questionnaire data from 206 outpatients with clinically stable bronchiectasis were used to develop the BHQ (Bronchiectasis Health Questionnaire). Responses to a 65-item questionnaire were used to establish the final 10-item version of the BHQ, which displayed good internal consistency (Cronbach's  $\alpha=0.85$ ) and high and moderate convergent validity with the St George's Respiratory Questionnaire and percent FEV<sub>1</sub>, predicted, respectively ( $r$  values  $-0.27$  and  $-0.82$  [ $p \leq 0.001$ ]). Significant associations were seen between BHQ score and number of bronchiectasis exacerbations in the prior 12 months, hospital admissions and bronchiectasis pulmonary lobe counts on CT ( $p < 0.001$  for all). Patients with sputum bacterial colonisation had significantly worse BHQ scores than noncolonised patients ( $p = 0.048$ ). Repeatability of the BHQ after 2 weeks was high (intraclass correlation coefficient 0.89).

**Comment:** Severity and prognosis of bronchiectasis can be gleaned from the BSI or FACED scores (Respiratory Research Review, [issue 106](#)). A group of European researchers developed, validated and translated a simple 10-item score to assess the QOL in patients with bronchiectasis. This new BHQ score is based on self-reported tiredness, slowness, anxiety, feeling of a clear chest, sputum production, shortness of breath, sleep disturbance, coughing fits and antibiotic treatment in the last 14 days. **Bottom line: the new BHQ score is a quick, 10-item, valid score to measure the QOL of patients with bronchiectasis in the clinic.**

**Reference:** *Eur Respir J* 2017;49(5):1601532

[Abstract](#)

## Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research

**Authors:** Hill AT et al.

**Summary:** Definitions used for bronchiectasis exacerbations in clinical trials between January 2000 and December 2015 were systematically reviewed by experts from Europe, North America, Australasia and South Africa, with the aim of reaching a consensus definition. The definition unanimously approved by the working group was a person with bronchiectasis with a deterioration in  $\geq 3$  key symptoms for  $\geq 48$  hours.

**Comment:** This article summarises the scientific process and findings of a group of international bronchiectasis experts, including our colleague Conroy Wong from Waitemata Health, to define an exacerbation in adult patients with significant bronchiectasis. Having a clearly defined definition will assist clinical trial work, because times between exacerbations or severity of exacerbation are important clinical endpoints. **Bottom line: an exacerbation of bronchiectasis is defined as three of the following key symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required.**


**Reference:** *Eur Respir J* 2017;49(6):1700051

[Abstract](#)

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## Bronchiectasis rheumatoid overlap syndrome is an independent risk factor for mortality in patients with bronchiectasis

**Authors:** De Soyza A et al.

**Summary:** This analysis examined data from six cohorts of patients (n=1716) from specialist bronchiectasis services around the world to determine if patients with BROS (bronchiectasis-rheumatoid overlap syndrome) have worse outcomes than those with bronchiectasis of other aetiologies by applying the BSI. BROS was significantly associated with mortality, although this relationship was not associated with increased bronchiectasis exacerbation or bronchiectasis-related hospitalisation rates. Over a mean 48-month follow-up, mortality rates were 9.3% for idiopathic bronchiectasis, 8.6% in patients with other causes of bronchiectasis, 18% for rheumatoid arthritis and 28.5% for BCOS (bronchiectasis-COPD overlap syndrome). BROS and BCOS were associated with significantly higher mortality than other bronchiectasis aetiologies. Compared with idiopathic bronchiectasis, BROS was associated with a statistically, but not clinically, significantly higher mean BSI score (7.7 vs. 7.1 [ $p<0.05$ ]). BCOS was associated with higher mean BSI score (10.4), *Pseudomonas aeruginosa* colonisation rate (24%) and previous hospitalisation rate (58%).

**Comment:** As mentioned in the introduction, bronchiectasis can occur in patients with respiratory illnesses like COPD, or with connective tissue disorders like rheumatoid arthritis without interstitial lung disease. The authors pooled data from six databases from the UK, Ireland and Belgium and discovered an overlap with COPD in 12%; these patients are more likely to be male, older and have a lower FEV<sub>1</sub>; their mortality rate at 2 years was 28.5%.

**Bottom line: a total of 8.5% of patients with bronchiectasis also had rheumatoid arthritis; their mortality at 2 years was 18%, about twice the mortality rate of idiopathic bronchiectasis.**

**Reference:** *Chest* 2017;151(6):1247–54

[Abstract](#)

## Bronchiectasis in yellow nail syndrome

**Authors:** Woodfield G et al.

**Summary:** These authors reported on 25 adult clinic patients with bronchiectasis who also had yellow-nail syndrome, each matched to two controls with idiopathic bronchiectasis. All patients with yellow-nail syndrome had chronic productive cough, 88% had chronic rhinosinusitis, 20% had pleural effusions and 12% had lymphoedema. In around two-thirds of patients, chest symptoms preceded yellow nails. Fourteen patients had improved nails at follow-up, although 23 had persistent abnormalities. Symmetrical, predominantly lower-lobe bronchiectasis was seen on high-resolution CT in both groups, but to a lower extent and severity, and with reduced bronchial wall thickness and upper and middle lobe disease, in patients with yellow-nail syndrome. Mucus plugging was also increased in patients with yellow-nail syndrome. The groups had similar prevalences of *Pseudomonas aeruginosa* infection and mild lung function abnormalities.

**Comment:** Yellow-nail syndrome is an intriguing, rare illness with two of the following three symptoms: yellow, slow-growing, cross-riding nails, lymphoedema and pulmonary manifestations of chronic cough, pleural effusions or chronic rhinosinusitis. This group from the Brompton identified 25 patients with yellow-nail syndrome and bronchiectasis. These patients had a median age of 58 years, mild airflow obstruction and bronchiectasis sparing the upper and middle lobes. All patients were treated with physiotherapy, and 80% of patients were offered clarithromycin 250mg three times weekly as a prophylactic antibiotic. **Bottom line: yellow-nail syndrome is a distinct cause of mild bronchiectasis involving mainly the lower lobes.**

**Reference:** *Respirology* 2017;22(1):101–7

[Abstract](#)

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## Effect of pulmonary exacerbations treated with oral antibiotics on clinical outcomes in cystic fibrosis

**Authors:** Stanojevic S et al.

**Summary:** The impact of milder pulmonary exacerbations treated with oral antibiotics (2608 events) on short-term clinical outcomes was investigated in a retrospective cohort of 570 patients with CF. Lung function was already  $\geq 90\%$  of baseline FEV<sub>1</sub> at the start of oral antibiotic therapy for 53.4% of events, and it was  $\geq 90\%$  of baseline at follow-up for 82% of events. Compared with no oral antibiotic-treated milder pulmonary exacerbation events in the prior 12 months, the occurrence of  $\geq 1$  such event was associated with a decreased FEV<sub>1</sub>. Cumulatively over the entire study period, patients who experienced  $\geq 6$  oral antibiotic-treated milder pulmonary exacerbation events had the steepest rate of FEV<sub>1</sub> decline. Oral antibiotic-treated milder pulmonary exacerbations were not associated with changes in body mass index.

**Comment:** Infective exacerbations in patients with CF are important events leading to a loss of FEV<sub>1</sub> in up to a third of patients. Severe exacerbations are defined as a hospital admission for intravenous antibiotics. Clinicians often treat milder exacerbations with oral antibiotics. This Canadian group from Toronto used a cohort of 570 children and 2600 exacerbations to explore the effect of milder exacerbations on lung function. The authors found a dose-response like relationship between the number of exacerbations treated with oral antibiotics and the loss of FEV<sub>1</sub>. **Bottom line: exacerbations treated with oral antibiotics have a negative short-term and cumulative effect on lung function.**

**Reference:** *Thorax* 2017;72(4):327–32

[Abstract](#)

### Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board.



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## Variation in lung function as a marker of adherence to oral and inhaled medication in cystic fibrosis

**Authors:** White H et al.

**Summary:** Adherence to CF treatment was evaluated in 249 patients aged  $\geq 16$  years with the disease to determine if lung function variability predicts adherence. The patients were categorised as  $<50\%$ ,  $50\text{--}80\%$  or  $\geq 80\%$  adherent according to composite medication possession ratio scores. Mean adherence according to medication possession ratio was 63%. An inverse relationship was seen between the coefficient of variation for FEV<sub>1</sub> and adherence at 6 and 12 months on univariate analysis (respective odds ratios 0.92 [95% CI 0.87, 0.98] and 0.94 [0.93, 0.99]); significance persisted in the final models. Neither bodyweight nor C-reactive protein level variability predicted adherence.

**Comment:** Poor adherence remains a significant challenge in the management of chronic diseases, including CF, where it may lead to pulmonary exacerbations, loss of QOL or hospital admissions. Here the research unit in Leeds enrolled 250 of their 400 CF patients to explore whether the variability in FEV<sub>1</sub> rather than the loss in FEV<sub>1</sub> could be a sensitive marker to reflect treatment adherence. The researchers compared the variability of FEV<sub>1</sub> with traditional measures like pill retrieval or self-reported adherence. **Bottom line: the variability in FEV<sub>1</sub> measurements is a significant predictor of adherence to treatment.**

**Reference:** *Eur Respir J* 2017;49(3):1600987

[Abstract](#)

## Efficacy and safety of lumacaftor and ivacaftor in patients aged 6–11 years with cystic fibrosis homozygous for F508del-CFTR

**Authors:** Ratjen F et al., on behalf of the show VX14-809-109 investigator group

**Summary:** Patients aged 6–11 years with CF (percent predicted FEV<sub>1</sub>  $\geq 70$  and lung clearance index<sub>2.5</sub>  $\geq 7.5$ ) and the F508del-CFTR (cystic fibrosis transmembrane conductance regulator) mutation on both alleles were stratified by bodyweight and percent predicted FEV<sub>1</sub> and randomised to receive lumacaftor 200mg and ivacaftor 250mg (evaluable n=103) or placebo (evaluable n=101) every 12 hours for 24 weeks in this phase 3 trial. For the lumacaftor plus ivacaftor versus placebo arms, there was a significant difference for least squares mean difference in average absolute change in: i) lung clearance index<sub>2.5</sub> between baseline and week 24 (primary endpoint;  $-1.09$  units [ $p<0.0001$ ]); ii) sweat chloride level at day 15/week 4 ( $-20.8$  mmol/L [ $p<0.0001$ ]); and iii) percent predicted FEV<sub>1</sub> out to week 24 ( $2.4$  [ $p=0.0182$ ]). Safety data were consistent with those in previous phase 3 trials of lumacaftor and ivacaftor.

**Comment:** Ivacaftor, a CFTR potentiator, is effective in class III channel abnormalities, where CFTR reaches the cell membrane but is not fully functional. In the 5% of the CF population with the CFTR mutation Gly551Asp, ivacaftor improves lung function, nutritional status and symptoms. Ivacaftor is not active in the most common homozygous class II mutation (Phe508del) with minimal or nonfunctional CFTR. The combination of ivacaftor with the potentiator lumacaftor led to mild/moderate side effects in almost half the group. **Bottom line: the combination of ivacaftor and lumacaftor is associated with a small improvement in lung function.**

**Reference:** *Lancet Respir Med* 2017;5(7):557–67

[Abstract](#)

References: 1. Noble PW, et al. *Eur Respir J* 2016;47:243–253 2. Esbriet® (pirfenidone) Data Sheet. Dated 26 September 2016 3. PHARMAC 2017. Application for subsidy by special authority, SA1628. Available at <http://www.pharmac.govt.nz/2017/01/01/SA1628.pdf>. Accessed 09 January 2017.

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## Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del

**Authors:** Taylor-Cousar JL et al.

**Summary:** Patients aged  $\geq 12$  years with CF who were homozygous for the Phe508del *CFTR* mutation were randomised to receive tezacaftor 100mg once daily and ivacaftor 150mg twice daily or matched placebo for 24 weeks in this phase 3 trial; 475 participants completed treatment. Compared with placebo recipients, tezacaftor plus ivacaftor recipients experienced a significant difference for the absolute and relative changes in percent predicted FEV<sub>1</sub> (4.0 and 6.8, respectively [ $p < 0.001$  for both]) and a 35% lower rate of pulmonary exacerbations ( $p = 0.005$ ). Adverse events were similar between the two groups, and most were of mild or moderate severity. There were fewer adverse respiratory events in the tezacaftor plus ivacaftor arm than in the placebo arm, and none led to discontinuation.

**Comment:** Ivacaftor alone is not active in patients with the common class II (Phe508del) *CFTR* mutation. The combination of lumacaftor and ivacaftor has only a modest benefit with side effects of cough, rhinorrhoea, nasal congestion and possible liver damage. Researchers here reported on the combination of a new corrector, tezacaftor, with ivacaftor. The active treatment group had improved FEV<sub>1</sub>, reduced exacerbations and improved QOL. However, Hartmut Grasemann gives a great overview in this accompanying [editorial](#) of gene defects, treatment options and our **bottom line: the current therapies for the most common CF mutation are still suboptimal.**

**Reference:** *N Engl J Med*; Published online Nov 3, 2017

[Abstract](#)

## Preparation for a first-in-man lentivirus trial in patients with cystic fibrosis

**Authors:** Alton EFW et al.

**Summary:** This paper reported on key translational, preclinical studies in preparation for a first-in-human trial using a lentiviral vector for *CFTR* gene delivery in patients with CF. The lead candidate was selected by assessing regulatory-compliant vectors that carried a range of promoter/enhancer elements in mice and human air-liquid interface cultures. It was assessed for *CFTR* expression and function in CF models, and its toxicity was assessed and 'benchmarked' against a leading nonviral formulation used in a recent phase 2b clinical trial. Clinical trial dose ranging was determined, and assessment of the impact of pre-existing and acquired immunity against the vector and vector stability in several clinically relevant delivery devices was performed. The lead candidate lentiviral vector was found to express functional *CFTR* and retained 90–100% transduction efficiency in relevant delivery devices. The authors commented that the efficacy ( $\geq 14\%$  of airway cells transduced), toxicity and integration-site profile findings support progression to clinical trials.

**Comment:** One of the rate-limiting steps of gene therapy in the management of CF is the search for a suitable vector to 'infect' respiratory epithelial cells with the corrected *CFTR* gene to express appropriate function. Adenovirus infections cause significant respiratory comorbidities, while nonviral formulations have a low targeted infection rate. In this paper, UK researchers detail the rationale and animal experiments exploring the safety and efficacy of lentivirus regional vector delivery to the airways. **Bottom line: the combination of viral vector production methods with mouse and ex vivo human data suggests first-in-human studies in CF could start.**

**Reference:** *Thorax* 2017;72(2):137–47

[Abstract](#)

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### Esbriet® Abridged Prescribing Information (API)

Esbriet (pirfenidone) 267 mg oral capsule is a **Prescription Medicine** indicated for the treatment of idiopathic pulmonary fibrosis (IPF). **Dosage and Administration:** Please see Esbriet Data Sheet for information. **Contraindications:** Contraindicated in patients with a hypersensitivity to pirfenidone or any of the excipients; Patients taking fluvoxamine and patients with a history of angioedema with pirfenidone. **Precautions:** **Hepatic Function:** Elevations in ALT and AST 3 x ULN have been reported. Liver function tests should be conducted prior to and during treatment. If significant elevations occur the dose of Esbriet should be adjusted, refer to dosage guidelines in Data Sheet. Caution when used in patients with mild to moderate hepatic impairment. **Photosensitivity reaction/rash:** exposure to direct sunlight should be minimised during treatment and patients instructed to wear sunblock and protective clothing. Dosage adjustment or temporary discontinuation may be required, refer to dosage guidelines in Data Sheet; **Angioedema:** patients who develop signs or symptoms of angioedema while taking Esbriet should immediately discontinue treatment. **Cigarette smoking and inducers of CYP1A2:** exposure to pirfenidone was 50% less in patients who were smokers, concomitant use of strong inducers of CYP1A2 including smoking should be avoided. **Pregnancy Cat B3:** there are no data on the use in pregnancy. **Paediatric:** safety has not been established. **Renal Impairment:** Use with caution in patients with mild, moderate or severe renal impairment. **Drug Interactions:** Esbriet is contraindicated in patients taking fluvoxamine and caution should be taken in patients taking inhibitors of CYP1A2 e.g. ciprofloxacin, amiodarone, propafenone or inducers of CYP1A2 e.g. omeprazole, rifampicin. **Adverse Effects:** (Common only: see Data Sheet for full list): Upper respiratory tract infection; urinary tract infection; weight decreased; decreased appetite; insomnia; dizziness; somnolence; dyspepsia; lethargy; hot flush; dyspnoea; cough; productive cough; gastroesophageal reflux disease; vomiting; abdominal distension; abdominal discomfort; abdominal pain; abdominal pain upper; stomach discomfort; gastritis; constipation; flatulence; ALT increased; AST increased; gamma glutamyl transferase increased; pruritus; erythema; dry skin; rash erythematous; rash macular; rash pruritic; myalgia; arthralgia; asthenia; non-cardiac chest pain; sunburn.

**ESBRIET is a funded medicine for patients with IPF who meet pre-defined criteria. Prescription and doctors' fees may apply.**

Before prescribing, please review the ESBRIET Data Sheet available at [www.medsafe.govt.nz](http://www.medsafe.govt.nz). API based on Data Sheet [26-09-2016]. Roche Products (New Zealand) Limited, Auckland. Ph 0800 656 464. [www.roche.co.nz](http://www.roche.co.nz) All trademarks mentioned herein are protected by law.

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