Healthcare providers:

1. **What is SERVE-HF?**

SERVE-HF is a multinational, multicenter, randomized controlled Phase IV study designed to assess whether treatment of moderate to severe predominant central sleep apnea with adaptive servo-ventilation (ASV) therapy, in addition to optimized medical care, could reduce mortality and morbidity in patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%).*

The study recruited a total of 1,325 subjects who were randomized to one of the two arms.
The details of the study can be found on https://clinicaltrials.gov/ct2/show/NCT00733343

2. **What were the results?**

Results showed no significant difference between patients randomized to ASV and those in the control group for the primary endpoint of time to all-cause mortality or unplanned hospitalization for worsening heart failure (based on a hazard ratio [HR] =1.13 , 95 percent confidence interval [95% CI] =(0.97, 1.31)), p-value= 0.10*). However, there is a statistically significant 2.6% absolute increased annual risk of cardiovascular mortality for those randomized to ASV therapy compared to the control group. In the study,* 10.2*% of the ASV group experienced a cardiovascular death each year compared to* 7.6*% of the control group, representing a* 34*% relative increased risk of cardiovascular mortality (HR=1.34, 95%CI=(1.09, 1.65), p-value=0.006).**

For more information on the final results, go to:
http://www.nejm.org/doi/full/10.1056/NEJMoa1506459 New England Journal of Medicine publication: Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure (SERVE-HF)". Martin R. Cowie, M.D., Imperial College London -- London, UK.

3. **Who is at risk?**

The patient population studied in the SERVE-HF trial is considered at risk for increased cardiac mortality. Specifically, that is patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) (New York Heart Association Classification Levels [NYHA] 2-4) on ASV therapy for predominantly central sleep apnea. *

4. **Should affected patients discontinue therapy?**

ResMed recommends that physicians contact their at-risk patients to discuss whether to discontinue treatment given that no benefit was observed in SERVE-HF patients treated with ASV, and there was an increased risk of cardiovascular mortality. The decision to discontinue ASV therapy is ultimately a clinical one.*

5. **Are the devices malfunctioning?**

There has been no malfunction or technical fault observed with ASV device operation; it operates correctly to treat predominant central sleep apnea.

The increased risk of cardiovascular death occurred in a scientific study (SERVE-HF) investigating the use of ASV therapy in people with moderate to severe predominant central sleep apnea and symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%). *

6. **How quickly should I ask ASV patients to stop therapy?**

We recommend you urgently contact those ASV patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea, to discuss immediate discontinuation of ASV treatment. *

7. **What should I do with new patients?**

ASV therapy is now contraindicated for patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea.*

8. **Does the risk change with time on therapy?**

Based on our assessment of the data from SERVE-HF, it appears that the risk for cardiovascular mortality in patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea, does not change with time on therapy and is independent of perceived benefit from therapy.*

9. **Does ASV mode with automatic EPAP have the same issue as the ASV mode with fixed EPAP?**

The devices used in the SERVE-HF trial had fixed EPAP, but we believe that automatic EPAP may also increase cardiovascular risk in patients with symptomatic chronic heart failure with reduced ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnea.*

10. **What about patients with cardiovascular diseases other than heart failure, who are using ResMed's ASV therapy. Are they at risk as well?**

The results of SERVE-HF cannot be extrapolated to patients with cardiovascular diseases other than heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea. SERVE-HF only investigated patients with symptomatic chronic heart failure patients with reduced EF and predominant central sleep apnea.*

11. **What about patients suffering from heart failure using continuous positive airway pressure (CPAP or APAP) for obstructive sleep apnea or a ventilation device for respiratory disorders? Are they at risk and should they be concerned?**

The results of SERVE-HF cannot be extrapolated to patients treated with CPAP, APAP or any other ventilation device.

12. My heart failure patients have fewer symptoms when using ResMed's ASV device. Does that mean ASV therapy is beneficial and they may be maintained on therapy?

The increased cardiovascular risk shown in SERVE-HF is independent of symptomatic improvement. We recommend you urgently contact those patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea, on ASV therapy to discuss with them immediate discontinuation of ASV treatment.*

For patients who have OSA, the physician may consider transitioning them to CPAP/APAP.

13. What should I do if my heart failure patient does not want to give up on the ASV therapy?

The patient population studied in the SERVE-HF trial is considered at risk for increased cardiac mortality; specifically patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45) and moderate to severe predominant central sleep apnea, on ASV therapy. Because of the increased mortality risk in the affected patient population, ResMed has updated the user guides and clinical manuals for its ASV devices to add a contraindication for use of this therapy with those patients.*

We recommend you urgently contact those patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea, currently on ASV therapy to discuss the immediate discontinuation of ASV treatment.

ResMed defers to the clinical judgment of physicians, in consultation with their patients, regarding the proper course of treatment for any particular patient based on that patient's condition, and whether a particular course of treatment should continue to involve ASV therapy. The decision to continue or discontinue therapy is for patients and their physicians to make. However, based on the results of SERVE-HF, ResMed has updated the user guides and clinical manuals for its ASV devices to add a contraindication for use of this therapy.*

14. Is therapy with PAP devices safe?

SERVE-HF has shown that treating central sleep apnea with adaptive servo-ventilation in patients with chronic heart failure with reduced ejection fraction is associated with an increased risk of cardiovascular mortality. This group of patients is a very small minority (less than 1%) of those using PAP devices. In addition to their use in the treatment of central sleep apnea, PAP devices are more commonly used for the treatment of OSA and respiratory insufficiency and failure. There is no evidence to suggest that the use of PAP devices in these clinical applications is associated with increased risk of cardiovascular events or death.

15. Are there patients that SHOULD stay on ASV?

There is no evidence to suggest that there is increased risk of cardiovascular death for patients with central sleep apnea or complex sleep apnea without symptomatic chronic heart failure and reduced ejection fraction.

User guides and clinical manuals for ResMed's ASV products have been updated to contraindicate the use of ASV in patients with symptomatic chronic heart failure with reduced ejection fraction (Left Ventricular Ejection Fraction [LVEF] ≤ 45%) and moderate to severe predominant central sleep apnea. Other indications for ASV therapy are unchanged.*

* ASV therapy is contraindicated in patients with chronic, symptomatic heart failure (NYHA 2–4) with reduced left ventricular ejection fraction (LVEF ≤ 45%) and moderate to severe predominant central sleep apnea.

Country	Hotline #
United States	1-800-478-9010
France	0805408804
UK	0800 917 9411
Ireland	
Germany	0800 2770400
Austria	+49 89 9901 0565
Sweden	+46 8477 10 00
Switzerland	0800 00 25 00
Norway	+47 800 33 100
Finland	+358 45 77310405
Italy	+39 344 0488702
Spain	+33426100349
Portugal	+33805408804
Czech Republic	+420 244 471 299
Poland	+48 22 121 6423
Netherlands	+441235 437580
Belgium	+33805408804 (Fr) +441235 437580 (NL + ENG)
Luxemburg	+33805408804 (Fr) +441235 437580 (NL + ENG)

India	+91 9958030808
Australia New Zealand	Australia: 1800 647 259 New Zealand: 0800 737 635
China	China hotline 400 810 6016 (toll free) Taiwan hotline +886 2 25568707
Singapore	+65 9128-8850
Malaysia	+60 16-688-5271
Thailand	+66 89-494-3020