on this information, Merck launched clinical trials designed to determine the efficacy of this compound for the treatment of major depressive disorder.

As part of these efforts, Merck also performed a series of PET imaging studies designed to determine the level of target engagement in the brain provided by clinical doses of this compound. In these experiments, patients were dosed initially with the L-829165-^{18}F (Figure 10.9(b)), a PET tracer ligand known to selectively bind to NK_1.[70] This was followed by treatment with the phase III clinical doses of Emend® used in the major depressive disorder trials. NK_1 receptor occupancy was then assessed via PET imaging based on displacement of the PET tracer ligand by the clinical candidate. The results of this study clearly demonstrated that up to 100% NK_1 receptor occupancy could be achieved with the clinical doses of Emend®, confirming target engagement. At the same time, however, clinical efficacy was *not* achieved. After 8 weeks of treatment, there was no significant difference between the treatment groups and placebo. In contrast, 20 mg of the antidepressant Paxil® (Paroxetine),[71] a selective serotonin reuptake inhibitor (SSRI), provides symptom relief after 8 weeks. The failure of the Emend® major depressive disorder clinical studies combined with the clear evidence of target engagement led to the conclusion that the NK_1 receptor is not a viable target for the treatment of depression. Although the PET imaging studies did not lead to a positive result, they did provide a better understanding of the limitations of NK_1 receptor antagonism and most likely prevented the further progression of additional NK_1 receptor antagonists into clinical studies. In the absence of the aforementioned PET imaging biomarker studies, it would have been difficult to determine if the failure of Emend® was compound-specific or target-related. Resources that could have been devoted to better therapeutic targets would have been wasted in pursuit of an effect that could never be achieved.

Identifying biomarkers that facilitate the characterization of candidate compounds can have a significant impact on the various stages of drug discovery and development. Biomarkers that are indicative of efficacy can shorten clinical trials and decrease the number of patients exposed to new compounds. Safety risks can also be mitigated by identifying biomarkers that are indicative of potential risks. Termination of clinical programs due to poor performance in biomarker studies, whether by virtue of efficacy issues or the identification of safety risks, allows resources to be quickly redirected to more fruitful areas, thereby adding efficiency to the drug discovery and development process. Bringing these tools together through the concepts of translation medicine in a "bench-to-bedside approach" can also improve the use of resources at the earliest stages of drug discovery. Biomarkers of efficacy in disease states can be used to determine the