GABAkines - Background
The first major class of drugs initially reported to act as GABA<sub>A</sub> PAMs were benzodiazepines (BDZ), such as Valium® and Xanax®. These drugs produce a wide range of pharmacological properties, including anxiety reduction, anti-convulsant and muscle relaxation. Unfortunately, they also produce sedation, respiratory depression, cognitive impairment, as well as tolerance, abuse and withdrawal. For this reason, concerns have been raised regarding the safety of widespread BDZ use.

KRM-II-81, our lead GABAkine, is the most advanced and druggable of a series of proprietary compounds that represent a new generation of GABAkines. Unlike BDZ, KRM-II-81 displays selectivity at α-2/3 GABA<sub>A</sub> receptor subtypes and, as a result, produces a unique spectrum of pharmacological activity with a high degree of specificity. It shows positive activity in animal models of epilepsy, pain, anxiety and depression, in the absence of or with greatly reduced liability to produce sedation, motor incoordination, cognitive impairments, respiratory depression, tolerance, abuse and withdrawal seizures, all side effects associated with BDZ. We currently are focused on the potential treatment of epilepsy and pain. Sixteen articles describing the results of these studies have been published in highly regarded peer reviewed journals, including three review articles and a book chapter detailing the anti-epileptic and analgesic properties of KRM-II-81 and its importance in the overall field of GABAkines.

EPILEPSY - Epilepsy is a chronic neurological disorder that affects millions of people world-wide and has serious consequences for the life of the affected individual. Pharmaco-resistance to anticonvulsant therapy continues to be one of the key obstacles to the treatment of epilepsy. Although many anticonvulsant drugs are approved to decrease seizure probability, seizures frequently are not fully controlled and patients are generally maintained daily on multiple antiepileptic drugs with the hope of enhancing the probability of seizure control. Despite this polypharmacy approach, as many as 60% to 70% of patients continue to have seizures and sometimes require surgical resection of targeted brain tissue.

KRM-II-81 has demonstrated efficacy greater than or at least comparable to standard of care treatments in multiple rodent models and measures of antiepileptic drug efficacy in vivo and ex vivo. This includes nine acute seizure provocation models in mice and rats, four seizure sensitization models in rats and mice, two models of chronic epilepsy, and three models specifically testing pharmaco-resistant epilepsy where standard of care medicines do not work. The anticonvulsant action of KRM-II-81 has been supported by microelectrode recordings from brain slices obtained from the freshly excised cortex tissue of epileptic patients, where in situ application of KRM-II-81 suppressed epileptiform electrical activity.

If the broad anti-epileptic properties of KRM-II-81 can be confirmed in patients, particularly treatment resistant patients, without developing tolerance, then KRM-II-81 would be a true breakthrough drug for the treatment of epilepsy.

PAIN - It is impossible not to be aware of the crisis that the opioid epidemic has created in the treatment of chronic pain. While there is no question as to their efficacy, the clinical use of opioids is severely limited due to the rapid development of tolerance, dependence and the production of opioid-induced respiratory depression, the major cause of opioid-induced lethality. Research programs are underway nationwide to discover and develop new non-opioid drugs that are effective analogues without the tolerance and abuse liability ascribed to opioids.

While BDZ are not known for their analgesic properties, the FDA approval of the GABAergic drugs, Neurontin® and Lyrica®, for the treatment of chronic pain is consistent with the idea that GABAergic neurotransmission is an important regulatory mechanism for the control of pain. Unfortunately, the clinical results have not been overwhelming with the most common side effects being sedation, dizziness and ataxia. It is uncertain whether greater efficacy was not observed because of poor intrinsic pharmacological efficacy or insufficient dosages due to dose limiting side effects.

KRM-II-81 has shown efficacy greater than or at least equal to standards of care in seven animal models of neuropathic and inflammatory pain in the relative absence of sedation, motor impairment, tolerance, physical dependence and abuse liability.

If the analgesic properties of KRM-II-81 can be confirmed in patients, without developing tolerance, it might also be a breakthrough drug for the relief of pain.

EndeavourRx is a stand-alone business unit of RespireRx, developing GABAkines and AMPAkines that act as positive allosteric modulators (PAMs) at GABA<sub>A</sub> and AMPA-type glutamate receptors, respectively.

The GABA<sub>A</sub> receptor is made up of five very heterogeneous, transmembrane proteins that form a pore allowing chloride to enter the cell. The unique α-2/3 GABA<sub>A</sub> receptor subtype selectivity of the GABAkines being developed by EndeavourRx offer the possibility of developing “kinder and gentler” drugs with greater pharmacological specificity and reduced side effects compared to present drugs, especially in disorders for which there is a significant unmet or poorly met clinical needs.

SUMMARY
- Broad anticonvulsant effects in animal models of epilepsy
- Broad analgesic effects in animal models of pain
- Active in animal models of anxiety and depression
- Lack of tolerance, physical dependence and abuse liability
- Reduced sedation and motor impairment
- Druggable and ready for further development
- Ready to begin IND enabling studies
- Patents claiming composition of matter, chemistry and method of treatment until 2036

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This communication shall not constitute an offer to sell or the solicitation of an offer to buy any securities, nor shall there be any sales of securities in any jurisdiction in which such offer, solicitation or sale of securities would be unlawful before registration or qualification under the laws of such jurisdiction.

Cautionary Note Regarding Forward-Looking Statements

This document contains certain forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the “Securities Act”) and Section 21E of the Securities Exchange Act of 1934, as amended (the “Exchange Act”), and the Company intends that such forward-looking statements be subject to the safe harbor created thereby. These might include statements regarding the Company’s future plans, targets, estimates, assumptions, financial position, business strategy and other plans and objectives for future operations, and assumptions and predictions about research and development efforts, including, but not limited to, preclinical and clinical research design, execution, timing, costs and results, future product demand, supply, manufacturing, costs, marketing and pricing factors.

In some cases, forward-looking statements may be identified by words including “assumes,” “could,” “ongoing,” “potential,” “predicts,” “projects,” “should,” “will,” “would,” “anticipates,” “believes,” “intends,” “estimates,” “expects,” “plans,” “contemplates,” “targets,” “continues,” “budgets,” “may,” or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words, and such statements may include, but are not limited to, statements regarding (i) future research plans, expenditures and results, (ii) potential collaborative arrangements, (iii) the potential utility of the Company’s product candidates, (iv) reorganization plans, and (v) the need for, and availability of, additional financing. Forward-looking statements are based on information available at the time the statements are made and involve known and unknown risks, uncertainties and other factors that may cause our results, levels of activity, performance or achievements to be materially different from the information expressed or implied by the forward-looking statements in this press release.

These factors include but are not limited to, regulatory policies or changes thereto, available cash, research and development results, issuance of patents, competition from other similar businesses, interest of third parties in collaborations with us, and market and general economic factors, and other risk factors disclosed in “Item 1A. Risk Factors” in the Company’s Annual Report on Form 10-K for the fiscal year ended December 31, 2021, as filed with the SEC on April 15, 2022 (the “2021 Form 10-K”) and other reports that we file with or furnish to the SEC.

You should read these risk factors and the other cautionary statements made in the Company’s filings as being applicable to all related forward-looking statements wherever they appear in this document. We cannot assure you that the forward-looking statements in this document will prove to be accurate and therefore prospective investors, as well as potential collaborators and other potential stakeholders, are encouraged not to place undue reliance on forward-looking statements. You should read this document completely. Other than as required by law, we undertake no obligation to update or revise these forward-looking statements, even though our situation may change in the future.

We caution investors, as well as potential collaborators and other potential stakeholders, not to place undue reliance on any forward-looking statement that speaks only as of the date made and to recognize that forward-looking statements are predictions of future results, which may not occur as anticipated. Actual results could differ materially from those anticipated in the forward-looking statements and from historical results, due to the risks and uncertainties described in the 2021 Form 10-K and other reports that we file with or furnish to the SEC that we may consider immaterial or do not anticipate at this time. These forward-looking statements are based on assumptions regarding the Company’s business and technology, which involve judgments with respect to, among other things, future scientific, economic, regulatory and competitive conditions, collaborations with third parties, and future business decisions, all of which are difficult or impossible to predict accurately and many of which are beyond the Company’s control. Although we believe that the expectations reflected in our forward-looking statements are reasonable, we do not know whether our expectations will prove correct. Our expectations reflected in our forward-looking statements can be affected by inaccurate assumptions that we might make or by known or unknown risks and uncertainties, including those described in the 2021 Form 10-K and in this document. These risks and uncertainties are not exclusive and further information concerning us and our business, including factors that potentially could materially affect our financial results or condition, may emerge from time to time.

For more information about the risks and uncertainties the Company faces, see “Item 1A. Risk Factors” in our 2021 Form 10-K. Forward-looking statements speak only as of the date they are made. The Company does not undertake and specifically declines any obligation to update any forward-looking statements or to publicly announce the results of any revisions to any statements to reflect new information or future events or developments. We advise investors, as well as potential collaborators and other potential stakeholders, to consult any further disclosures we may make on related subjects in our annual reports on Form 10-K and other reports that we file with or furnish to the SEC.