Figure 3: PVRI Change From Baseline By Treatment Group (Intent-to-Treat)

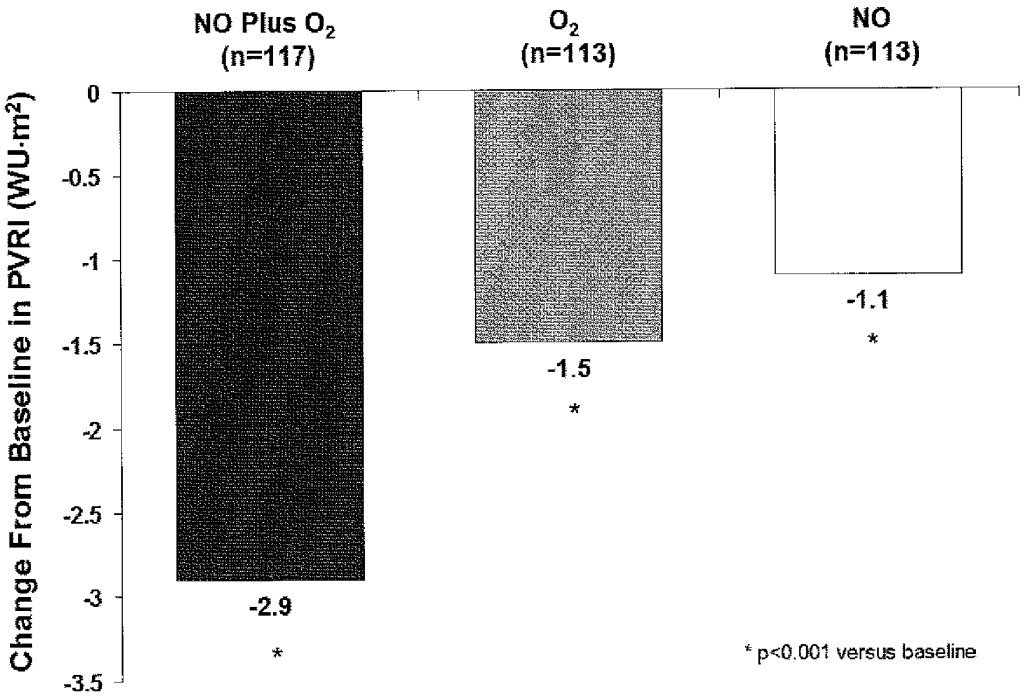


Table 15: PVRI Change From Baseline By Treatment (Intent-to-Treat)

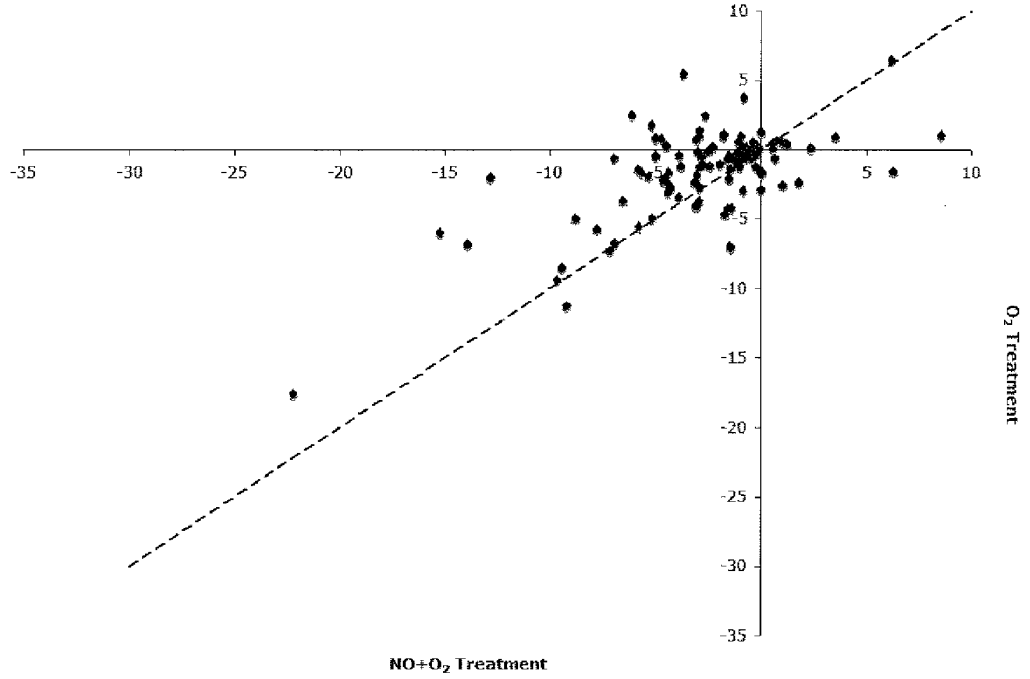
	Treatment		
PVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=117)**	**O_2 (n=113)**	**NO (n=113)**
Baseline (room air)			
Mean	10.8	10.0	10.3
SD	10.30	9.65	10.33
Median	7.5	6.9	6.6
Minimum, maximum	0.5, 54.0	0.5, 47.7	0.9, 54.0
Post-treatment			
Mean	7.8	8.5	9.2
SD	8.75	8.63	10.45
Median	3.6	5.5	5.6
Minimum, maximum	0.0, 44.8	0.5, 36.5	-6.3, 55.3
Change From Baseline			
Mean	-2.9	-1.5	-1.1
SD	4.75	3.13	3.04
Median	-1.8	-0.7	-0.8
Minimum, maximum	-31.2, 8.6	-17.6, 6.5	-10.0, 5.3
p-value[a]	<0.001	<0.001	<0.001
Pairwise comparisons NO plus O_2 versus O_2, p<0.001 NO plus O_2 versus NO, p<0.001 O_2 versus NO, p=0.171			

[a] p-value from a Wilcoxen Signed Rank test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.1.1 and Appendix 16.2.6

Results for the per-protocol population supported those for the intent-to-treat population. In the per-protocol population, the mean changes from baseline with NO plus O_2, O_2 and NO were -3.8 (p<0.001), -1.9 (p<0.001), and -1.1 (p=0.025) $WU \cdot m^2$, respectively.

Figure 4: PVRI Change From Baseline NO Plus O_2 Versus O_2 Alone (Intent-to-Treat)



The mean percent changes from baseline in PVRI for the intent-to-treat population (Table 16 and Figure 5) were -29.6%, -15.2%, and -15.9% for NO plus O2, O2, and NO, respectively (all p<0.001 versus baseline).

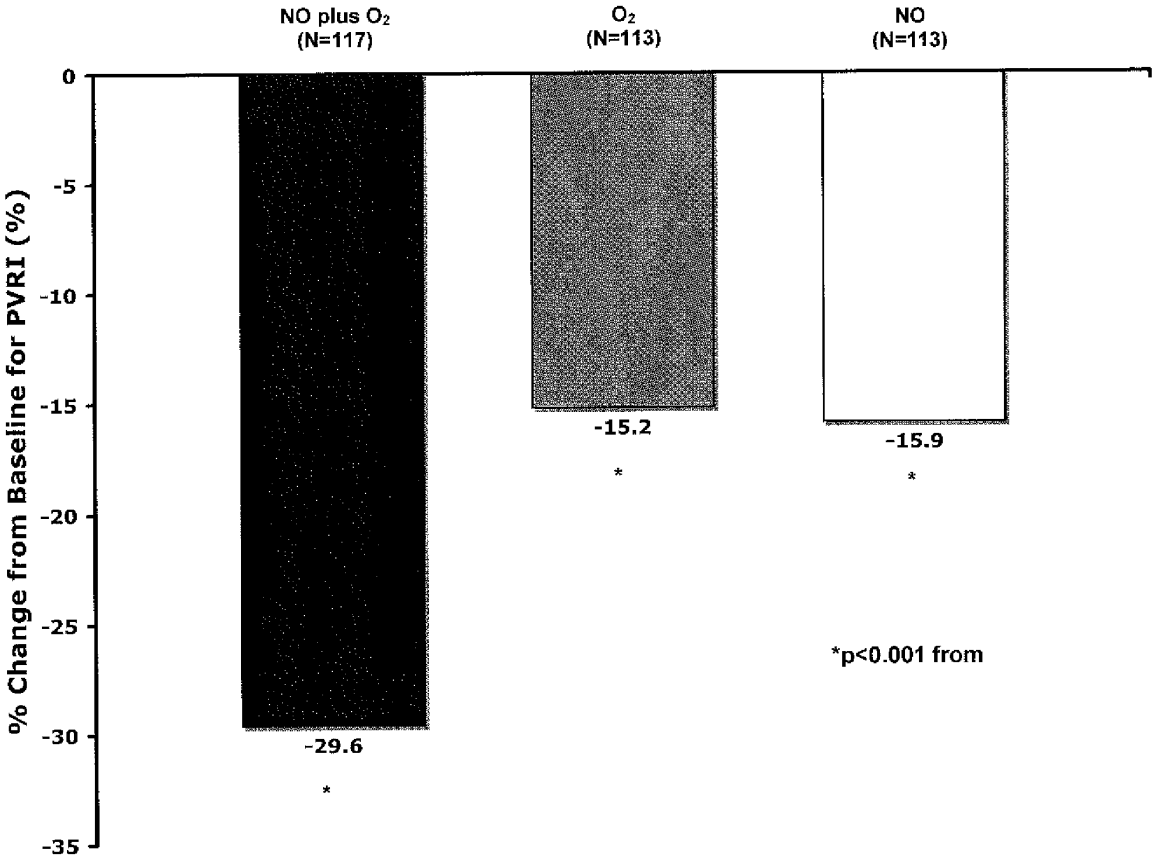
Table 16: PVRI Percent Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
PVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=117)**	**O_2 (n=113)**	**NO (n=113)**
Baseline (room air)			
Mean	10.8	10.0	10.3
SD	10.30	9.65	10.33
Median	7.5	6.9	6.6
Minimum, maximum	0.5, 54.0	0.5, 47.7	0.9, 54.0
Post-treatment			
Mean	7.8	8.5	9.2
SD	8.75	8.63	10.45
Median	3.6	5.5	5.6
Minimum, maximum	0.0, 44.8	0.5, 36.5	-6.3, 55.3
Percent Change From Baseline			
Mean	-29.6	-15.2	-15.9
SD	38.74	29.23	43.35
Median	-30.8	-14.8	-15.5
Minimum, maximum	-102.7, 201.1	-73.1, 89.7	-270.7, 117.7
p-value[a]	<0.001	<0.001	<0.001
Pairwise comparisons NO plus O_2 versus O_2, p=0.001 NO plus O_2 versus NO, p=0.002 O_2 versus NO, p=0.915			

[a] p-value from a Wilcoxen Signed Rank test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.1.3 and Appendix 16.2.6

Figure 5: PVRI Percent Change From Baseline by Treatment (Intent-to-Treat)



The mean percent changes from baseline in PVRI for the per-protocol population were -26.7% ($p<0.001$), -12.5% ($p<0.001$), and -7.8% ($p = 0.011$), respectively, for NO plus O_2, O_2, and NO.

Changes from baseline in PVRI for patients without shunts in both the intent-to-treat and the per-protocol populations were generally consistent with those for all patients in the respective populations.

Percent changes from baseline in PVRI for patients without shunts in both the intent-to-treat and the per-protocol populations were generally consistent with those for all patients in the respective populations.

All treatments also significantly decreased PAPm in the intent-to-treat population (Table 17). The mean changes from baseline in PAPm were -7.1, -3.5, and -4.1 mm Hg for NO plus O_2, O_2, and NO, respectively (all $p<0.001$ versus baseline).

Table 17: PAPm Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
PAPm (mm Hg)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	45.3	44.2	45.0
SD	16.78	16.30	17.57
Median	41.8	41.7	40.7
Minimum, maximum	17.0, 93.0	16.7, 88.7	14.0, 113.0
Post-treatment			
Mean	38.3	40.7	41.0
SD	16.38	14.57	17.94
Median	34.7	38.7	37.2
Minimum, maximum	12.7, 84.0	26.0, 85.0	16.0, 89.0
Change From Baseline			
Mean	-7.1	-3.5	-4.1
SD	8.25	8.10	7.51
Median	-5.3	-2.3	-2.8
Minimum, maximum	-36.0	-37.3, 17.7	-50.3, 9.0
p-value[a]	<0.001	<0.001	<0.001
Pairwise comparisons NO plus O_2 versus O_2, p<0.001 NO plus O_2 versus NO, p<0.001 O_2 versus NO, p=0.637			

[a] p-value from a Wilcoxen Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.2.1 and Appendix 16.2.6

All treatments also significantly decreased PAPm in the per-protocol population. The mean changes from baseline in PAPm were -7.6, -4.2, and -3.8 mm Hg for NO plus O_2, O_2, and NO, respectively (all p<0.001 versus baseline).

Results for patients without shunts in the intent-to-treat and per-protocol populations generally matched those for all patients in the respective populations.

Results for the intent-to-treat population indicated no differences among treatments with respect to changes from baseline in CO (Table 18). The mean changes from baseline in CO were 0.0 mL/minute for each treatment.

Table 18: CO Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
CO (mL/minute)	**NO Plus O_2 (n=112)**	**O_2 (n=109)**	**NO (n=109)**
Baseline (room air)			
Mean	2.3	2.2	2.3
SD	1.43	1.37	1.35
Median	1.9	1.9	2.0
Minimum, maximum	-2.5, 6.8	-2.5, 5.9	0.4, 6.8
Post-treatment			
Mean	2.2	2.2	2.4
SD	1.29	1.27	1.34
Median	2.0	1.9	2.0
Minimum, maximum	0.2, 6.4	0.4, 5.1	0.4, 7.4
Change From Baseline			
Mean	0.0	0.0	0.0
SD	1.01	0.70	0.88
Median	-0.1	-0.1	0.0
Minimum, maximum	-5.7, 5.1	-2.9, 4.6	-5.5, 4.5
p-value[a]	0.049	0.132	0.614
Pairwise comparisons NO plus O_2 versus O_2, p=0.979 NO plus O_2 versus NO, p=0.267 O_2 versus NO, p=0.259			

[a] p-value from a Wilcoxen Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.3.1 and Appendix 16.2.6

Results for the per-protocol population also indicated no differences among treatments with respect to changes from baseline in CO. The mean changes from baseline in CO were 0.0 mL/minute for each treatment.

Results for patients without shunts in the intent-to-treat and per-protocol populations generally matched those for all patients in the respective populations.

Results for the intent-to-treat population indicated that treatment with NO plus O_2 and O_2 alone significantly increased SVRI (Table 19). The change from baseline for NO plus O_2 was 1.4 $WU \cdot m^2$ ($p = 0.007$) and that for O_2 was 1.3 $WU \cdot m^2$ ($p = 0.004$). The change from baseline in SVRI with NO was -0.2 $WU \cdot m^2$ ($p = 0.889$).

Table 19: SVRI Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
SD	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxen Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: Section 14.2.2, Table 6.4.1 and Appendix 16.2.6

Results for the per-protocol population supported those for the intent-to-treat population. In this population, treatment with NO plus O_2 and O_2 alone also significantly increased SVRI. The change from baseline for NO plus O_2 was 1.5 WU·m^2 ($p = 0.037$) and that for O_2 was 1.4 WU·m^2 ($p = 0.012$). The change from baseline in SVRI with NO was 0.3 WU·m^2 ($p = 0.425$).

Effects of treatment on CO in patients without shunts in the intent-to-treat and per-protocol populations were similar to those for all patients in the respective study populations.

Treatment with NO plus O_2 resulted in a significantly lower PAPm to MAP ratio than O_2 alone (Table 20). These values were 0.60 and 0.64, respectively, for NO plus O_2 and O_2 only ($p<0.001$).

First Table added per request – (Table20b from e-mail)

Table 20: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

1 Wilcoxon Signed Rank Test
Source: Deb to confirm

2nd Table Added: (Table 20a from e-mail)

Table 220: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

1 Wilcoxon Signed Rank Test
Source: Deb to confirm

There was no difference in the PAPm to MAP ratios for NO plus O_2 and O_2 alone in the per-protocol population. This value was 0.71 for both NO plus O_2 and O_2 only ($p = 0.094$).

Results for patients without shunts in the intent-to-treat and per-protocol populations were consistent with those from all patients in the respective populations.

11.4.4. Statistical/Analytical Issues

11.4.4.1. Adjustments for Covariates

No adjustments were made for covariates.

11.4.4.2. Handling of Dropouts or Missing Data

There was no imputation of missing data. For the tabulations of demographics and efficacy statistics, patients with missing data were not included in the denominator for the calculation of any frequency percentages.

The denominator for concomitant medications and all adverse events was the total number of patients in the treatment group, regardless of any missing data.

11.4.4.3. Interim Analyses and Data Monitoring

Interim analyses for this study were performed periodically for the Steering Committee to review.

11.4.4.4. Multicenter Studies

No adjustments in the data analysis were made with respect to this variable.

11.4.4.5. Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons are necessary. The primary efficacy analysis was performed on the primary endpoint comparing the two treatment groups of interest. Other statistical tests to compare other treatment groups and secondary endpoints are provided as supportive data only.

11.4.4.6. Use of an "Efficacy Subset" of Patients

Intent-to-treat patients were all patients randomized regardless of actual receipt of any treatment gas, the treatment gas actually received, or the appropriateness of their enrollment. Efficacy analyses were also performed on the per-protocol population, since > 5% of the patients had baseline pulmonary vascular resistance index (PVRI) > 3 $WU \cdot m^2$ and actually took study medication. The per-protocol population included all patients who took study medication and had baseline PVRI >3 $WU \cdot m^2$.

11.4.4.7. Active-Control Studies Intended to Show Equivalence

This study had an active comparator, but was not intended to show equivalence.

11.4.4.8. Examination of Subgroups

There was no significant difference in pulmonary vasoreactivity for patients without shunts versus the entire study group in either the intent-to-treat or per-protocol populations. This was also the case for all secondary efficacy variables.

11.4.5. Tabulation of Individual Response Data

[To be provided]

11.4.6. Drug Dose, Drug Concentration, and Relationship to Response

Not applicable

11.4.7. Drug-Drug and Drug-Disease Interactions

Not applicable

11.4.8. By-Patient Displays

[To be provided]

11.4.9. Efficacy Conclusions

Results for the primary efficacy variable indicated that for the intent-to-treat population, NO plus O_2 resulted in a significantly higher pulmonary vasoreactivity response rate (25.7%) versus O_2 only (14.7%) ($p = 0.019$). In addition, 17.4% of patients responded only to NO plus O_2 versus 6.4% who responded to O_2 only.

A considerable proportion of randomized patients (36.6%) did not meet the entry criteria for PVRI > 3 units at baseline. For this reason, a per-protocol analysis was performed as well. For each of the pairwise comparisons noted above, the treatment effect was of similar or greater magnitude and in the same direction as for the ITT population. These results were generally not statistically significant due to the smaller sample size.

We note that seven patients (6.4%) responded to 100% O_2 but **did not** respond to NO 80 ppm with 90% O_2, which seems illogical. These seven patients were reviewed individually.

Table 21: Patients that responded only to 100% Oxygen

Pt Number	%Δ PVRI **O_2**	%Δ PVRI **O_2+NO**	%Δ PVRI **NO**	Comment
1004	-58.6%	-39.9%	+51.7%	CI -5.2%

Pt Number	%Δ PVRI O_2	%Δ PVRI O_2+NO	%Δ PVRI NO	Comment
1015	-25.6%	-27.3%	+10.57%	CI -7.0%
1026	-42.8%	-19.2%	+61.5%	2nd baseline very high
2007	-25.7%	-73.3%	-39.6%	CI -25.91%
3006	-45.9%	+48.2%	+117.7	BL PVRI 1.33
6005	-39.5	-55.5	-10.8	mPAP -19.4%
10003	-32.6	-6.7	+10.45%	

- Patient 1004 was a 5-month-old baby boy with a 39.9% reduction in PVRI on the combination regimen, but dropped the CI by 5.2%, greater than the 5% limit set by the response criteria. In absolute terms, this was a reduction of CI from 8.65 to 8.11 L/m/M^2, which is within the measurement error of the procedure[14].
- Patient 1015 was an 8.7-year-old girl with a 27.3% reduction in PVRI, but dropped the CI by 7.0% (1.95 to 1.81 L/m/M^2).
- Patient 1026 was a 2 ½-month-old baby girl that had O_2 alone in the third treatment period. In this patient, the second baseline value for PVRI (prior to the O_2 alone treatment period) was much higher than the initial baseline PVRI (4.525 WU·m^2 vs 6.755 WU·m^2), indicating that the patient was not at baseline when the final PVRI value was obtained.
- Patient 2007 was a 5-month-old baby boy requiring supplemental oxygen at baseline; the patient demonstrated a large decrease in PVRI and PAP, but a large drop in CI as well, without other obvious explanation.
- Patient 3006 was a 6-month-old baby boy with near-normal PVRI at first baseline (1.334 WU·m^2); this patient had O_2 alone in the first treatment period. In the first period there was a large percentage drop in PVRI, followed by a continual rise in PVRI, accompanied by a decrease in the CI over the subsequent periods. It is not clear if these changes are related to treatment, patient factors or procedural factors.
- Patient 6005 was an 8.6-year-old boy with CHD without a shunt, on supplemental oxygen at baseline. In this case, response criteria require a decrease in PAPm of ≥20%. In this case, the reduction in PVRI was 55.5%, but the reduction in PAPm was 19.4%, less than the 20% criterion.
- Patient 10003 was a 10.6-year-old boy on supplemental oxygen at baseline. This patient met response criteria to O_2 alone in the first period, without response to the other treatments in period 2 and period 3, without other obvious explanation.

Looking at these patients individually, we see that 4 of the 7 had more than adequate reduction in PVRI or PAP to qualify as responders to NO with O_2 but missed other elements of the response criteria; one patient was not at equilibrium during the procedure, and 2 are unexplained. There do

not appear to be commonalities among these patients with regard to center, diagnosis, age, race or sequence of treatment. None of these patients reported an AE.

There was no significant difference between pulmonary vasoreactivity response rates for NO alone versus O_2 alone in the intent-to-treat population (23.6% versus 15.1%, p=0.117), although numerically more patients were responders with NO alone as compared with O_2 alone. For this comparison, 19.8% of patients responded only to NO versus 11.3% for O_2 only. Comparison of results for NO and NO plus O_2 in the intent-to-treat population also indicated no significant differences in pulmonary vasoreactivity response. The response rate for NO was 24.1% and that for NO plus O_2 was 26.8% (p=0.602). In this comparison, 13.9% of patients responded only to NO versus 16.7% for NO plus O_2.

There was no significant difference in pulmonary vasoreactivity among patients with or without shunts, with or without intubation (an indicator of general anesthesia rather than simple sedation), in either the intent-to-treat or per-protocol populations. In the intent-to-treat population, 45.9% of patients with shunts responded versus 46.2% of those without shunts (p=1.000). There was no appreciable difference in response rates by treatment in patients with or without shunts. Patients with cardiomyopathy as the primary diagnosis seemed to respond more often than those with IPAH or CHD, but the number of those patients is too small to influence the overall results.

All treatments significantly decreased PVRI. In the intent-to-treat population, the mean changes from baseline with NO plus O_2, O_2, and NO were -2.9, -1.5, and -1.1 $WU \cdot m^2$, respectively (all p<0.001 versus baseline). The mean percent changes from baseline in PVRI for the intent-to-treat population were -29.6%, -15.2%, and -15.9% for NO plus O_2, O_2, and NO, respectively (all p<0.001 versus baseline).

All treatments also significantly decreased PAPm in the intent-to-treat population. The mean changes from baseline in PAPm were -7.1, -3.5, and -4.1 mm Hg for NO plus O_2, O_2, and NO, respectively (all p<0.001 versus baseline).

In the intent-to-treat population, there were no differences in mean changes from baseline in CO (0.0 mL/minute for each treatment).

Results for the intent-to-treat population indicated that treatment with NO plus O_2 and O_2 alone significantly increased SVRI. The change from baseline for NO plus O_2 was 1.4 $WU \cdot m^2$ (p=0.007) and that for O_2 was 1.3 $WU \cdot m^2$ (p=0.004). The change from baseline in SVRI with NO was -0.2 $WU \cdot m^2$ (p=0.899). Given the decrease in PAPm, this suggests that inhaled NO, alone or with O_2 is selective for the pulmonary vascular bed. This is further reflected in the change in ratio between the PA pressures and the systemic pressures. Treatment with NO plus O_2 resulted in a significantly lower PAPm to MAP ratio than O_2 alone. These values were 0.62 and 0.66 for NO plus O_2 and O_2 only (p=0.001). The reduction from baseline in the ratio of PAPm to MAP for NO with O_2 is 17.7%, as compared with a reduction of 10.6% and 7.8% for O_2 alone and NO alone, respectively. Thus we can conclude that inhaled nitric oxide (alone or with oxygen) is a selective pulmonary vasodilator. Not confirmed – DR.

12. SAFETY EVALUATION

12.1. Extent of Exposure

Exposure to NO plus O_2, NO, and O_2 is summarized in Table 4. The mean durations of exposure to NO plus O_2, NO, and O_2 were 15.5 minutes, 15.3 minutes, and 15.9 minutes, respectively.

12.2. Adverse Events

12.2.1. Brief Summary of Adverse Events

Seven patients experienced AEs during this study. These included cardiac arrest, bradycardia, low CO output syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH.

12.2.2. Display of Adverse Events

12.2.2.1. All-causality Adverse Events

Seven patients experienced AEs during this study (Table 22). These included cardiac arrest, bradycardia, low CO output syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH. The numbers of patients and events are too small to determine whether risk for AEs differed by diagnosis.

Table 22: Adverse Events By Diagnosis (Safety)

	Diagnosis			
System Organ Class/Preferred Term (n [%])[a]	**IPAH (n=28)**	**Cardiomyopathy (n=5)**	**CHD (n=91)**	**Overall (n=124)**
Patients With at Least One AE	0 (0.0)	1 (20.0)	6 (6.6)	7 (5.6)
Cardiac Disorders	0 (0.0)	0 (0.0)	3 (3.3)	3 (2.4)
Bradycardia	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.6)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Low CO Syndrome	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Investigations	0 (0.0)	1 (20.0)	2 (2.2)	3 (2.4
ECG ST Segment Elevation	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.6)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (1.1)	2 (1.6)
Hypotension	0 (0.0)	0 (0.0)	1 (1.1)	2 (1.6)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
PH	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.1 and Appendix 16.2.7

Adverse events are summarized by diagnosis and age in Table 23, diagnosis and gender in Table 24, and diagnosis and race in Table 25. Overall, AEs occurred more often in patients ≤ 10 years of age (6.7%) than in those >10 years old (2.9%). They also occurred more often in whites (9.6%) versus other races (0.0%). Patient gender had no effect on the incidence of adverse events; 4.8% of males and 6.5% of females experienced at least one AE.

Table 23: Adverse Events By Diagnosis and Age (Safety)

	Diagnosis and Age Group							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**≤10 years** (n=17)	**>10 Years** (n=11)	**≤10 years** (n=4)	**>10 Years** (n=1)	**≤10 years** (n=68)	**>10 Years** (n=23)	**≤10 years** (n=89)	**>10 Years** (n=35)
Patients With at Least One AE	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	5 (7.4)	1 (4.3)	6 (6.7)	1 (2.9)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	1 (4.3)	2 (2.2)	1 (2.9)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (4.3)	1 (1.1)	1 (2.9)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (2.9)	0 (0.0)	3 (3.4)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.2)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.2 and Appendix 16.2.7

Table 24: Adverse Events By Diagnosis and Gender (Safety)

	Diagnosis and Gender							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**Male (n=15)**	**Female (n=13)**	**Male (n=3)**	**Female (n=2)**	**Male (n=44)**	**Female (n=47)**	**Male (n=62)**	**Female (n=62)**
Patients With at Least One AE	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	3 (6.8)	3 (6.4)	3 (4.8)	4 (6.5)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	1 (2.1)	2 (3.2)	1 (1.6)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.1)	1 (1.6)	1 (1.6)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	2 (4.3)	0 (0.0)	3 (4.8)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	2 (3.2)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.3 and Appendix 16.2.7

Table 25: Adverse Events By Diagnosis and Race (Safety)

	Diagnosis and Race							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**White (n=19)**	**All Other (n=9)**	**White (n=3)**	**All Other (n=2)**	**White (n=51)**	**All Other (n=40)**	**White (n=73)**	**All Other (n=51)**
Patients With at Least One AE	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	6 (11.8)	0 (0.0)	7 (9.6)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (5.9)	0 (0.0)	3 (4.1)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Gastrointestinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Mouth Hemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (3.9)	0 (0.0)	3 (4.1)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 8.4 and Appendix 16.2.7

12.2.2.2. Adverse Events Related to Study Drug

A total of four patients had AEs that were related to study drug (Table 26). These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH, and hypotension.

Table 26: Adverse Events Related to Study Drug By Diagnosis (Safety)

	Diagnosis			
System Organ Class/Preferred Term (n [%])[a]	**IPAH (n=28)**	**Cardiomyopathy (n=5)**	**CHD (n=91)**	**Overall (n=124)**
Patients With at Least One AE Related to Study Drug	0 (0.0)	1 (20.0)	3 (3.3)	4 (3.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	2 (2.2)	2 (1.6)
Bradycardia	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Low CO Syndrome	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Investigations	0 (0.0)	1 (20.0)	1 (1.1)	2 (1.6)
ECG ST Segment Elevation	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
PH	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Vascular Disorders	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
Hypotension	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.1 and Appendix 16.2.7

Treatment-related AEs are summarized by diagnosis and age in Table 27. Overall, treatment-related AEs occurred more often in patients ≤ 10 years of age than in those >10 years old. However, there were only four treatment-related AEs, so any conclusions regarding effects of age must be viewed as highly speculative.

Table 27: Adverse Events Related to Study Drug By Diagnosis and Age (Safety)

	Diagnosis and Age Group							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])*	≤10 years (n=17)	>10 Years (n=11)	≤10 years (n=4)	>10 Years (n=1)	≤10 years (n=68)	>10 Years (n=23)	≤10 years (n=89)	>10 Years (n=35)
Patients With at Least One AE Related to Study Drug	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (2.9)	1 (4.3)	3 (3.4)	1 (2.9)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	1 (4.3)	1 (1.1)	1 (2.9)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	0 (0.0)	1 (2.9)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

* System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.2 and Appendix 16.2.7

Treatment-related AEs are summarized by diagnosis and gender in Table 28. Two treatment-related AEs occurred in males (3.2%) and two in females (3.2%).

Table 28: Adverse Events Related to Study Drug by Diagnosis and Gender (Safety)

	Diagnosis and Gender							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	**Male (n=15)**	**Female (n=13)**	**Male (n=3)**	**Female (n=2)**	**Male (n=44)**	**Female (n=47)**	**Male (n=62)**	**Female (n=62)**
Patients With at Least One AE Related to Study Drug	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	2 (4.5)	1 (2.1)	2 (3.2)	2 (3.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.5)	0 (0.0)	2 (3.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)		2 (3.2)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.3 and Appendix 16.2.7

Treatment-related AEs are summarized by diagnosis and race in Table 29. All four treatment-related AEs occurred in whites (5.5%).

Table 30: Adverse Events Related to Study Drug By Diagnosis and Race (Safety)

	Diagnosis and Race							
	IPAH		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	White (n=19)	All Other (n=9)	White (n=3)	All Other (n=2)	White (n=51)	All Other (n=40)	White (n=73)	All Other (n=51)
Patients With at Least One AE Related to Study Drug	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	3 (5.9)	0 (0.0)	4 (5.5)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
O_2 Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 10.4 and Appendix 16.2.7

12.2.3. Analysis of Adverse Events

All treatments were well-tolerated. Seven patients experienced AEs during this study and four of these were considered treatment-related. The adverse events included cardiac arrest, bradycardia, low CO syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH. The numbers of patients and events are too small to determine whether risk for AEs differed by diagnosis, age, gender, or race.

12.2.4. Listing of Adverse Events by Patient

A list of all AEs is provided in Table 30. Four of the seven AEs were mild or moderate in intensity and resolved. There were two severe AEs (low CO syndrome and hypertension, experienced by a single patient) that resulted in death.

Table 31: Adverse Events (Safety)

Patient Number	Age (years)	Race	Adverse Event	Serious	Severity	Relation to Study Drug	Outcome of Event
1007	0.7	White	Mouth hemorrhage	No	Moderate	Remote	Resolved
1020	0.8	White	O_2 saturation decreased	No	Mild	Possible	Resolved
4003	8.4	White	Hypotension	Yes	Moderate	Probable	Resolved
			ST segment elevation	Yes	Moderate	Probable	Resolved
4008	3.4	White	Low CO output syndrome	Yes	Severe	Probable	Fatal
		White	Hypertension	Yes	Severe	Probable	Fatal
6010	0.4	White	Hypotension	No	Mild	Not related	Resolved
17002	15.6	White	Bradycardia	No	Mild	Highly probable	Resolved
			Bradycardia	No	Mild	Highly probable	Resolved
5002	0.3	White	Bradycardia	Yes	Severe	Not related	Fatal
			O_2 saturation decreased	Yes	Severe	Not related	Fatal
			Cardiac arrest	Yes	Severe	Not related	Fatal

Source: Appendix 16.2.7

12.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1. Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

12.3.1.1. Deaths

Narratives for deaths are provided in Section 12.3.2.

12.3.1.2. Other Serious Adverse Events

Table 292: Serious Adverse Events By Diagnosis (Safety)

	Diagnosis			
System Organ Class/Preferred Term (n [%])[a]	**IPAH (n=28)**	**Cardiomyopathy (n=5)**	**CHD (n=91)**	**Overall (n=124)**
Patients With at Least One SAE	0 (0.0)	1 (20.0)	2 (2.2)	3 (2.4)
Cardiac Disorders	0 (0.0)	0 (0.0)	2 (2.2)	2(1.6)
Bradycardia	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Cardiac Arrest	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Low CO Syndrome	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Investigations	0 (0.0)	1 (20.0)	1 (1.1)	2 (1.6)
ECG ST Segment Elevation	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
PH	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.8)
Vascular Disorders	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)
Hypotension	0 (0.0)	1 (20.0)	0 (0.0)	1 (0.8)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.1 and Appendix 16.2.7

Serious AEs are presented by diagnosis and age, gender, and race in Tables 32, 33, and 34, respectively. Given the fact that only three patients experienced SAEs, no conclusions can be drawn from these analyses.

Table 303: Serious Adverse Events By Diagnosis and Age (Safety)

	Diagnosis and Age Group							
	Idiopathic		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	≤10 years (n=17)	>10 Years (n=11)	≤10 years (n=4)	>10 Years (n=1)	≤10 years (n=68)	>10 Years (n=23)	≤10 years (n=89)	>10 Years (n=35)
Patients With at Least One SAE	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	2 (2.9)	0 (0.0)	3 (3.4)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.9)	0 (0.0)	2 (2.2)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	1 (1.5)	0 (0.0)	2 (2.2)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.2 and Appendix 16.2.7

Table 314: Serious Adverse Events By Diagnosis and Gender (Safety)

	Diagnosis and Gender							
	Idiopathic		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	Male (n=15)	Female (n=13)	Male (n=3)	Female (n=2)	Male (n=44)	Female (n=47)	Male (n=62)	Female (n=62)
Patients With at Least One SAE	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	1 (2.3)	1 (2.1)	1 (1.6)	2 (3.2)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	1 (2.1)	1 (1.6)	1 (1.6)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (3.2)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (1.6)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.3)	0 (0.0)	1 (1.6)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)
Hypotension	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.6)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.3 and Appendix 16.2.7

Table 325: Serious Adverse Events By Diagnosis and Race (Safety)

	Diagnosis and Race							
	Idiopathic		Cardiomyopathy		CHD		Overall	
System Organ Class/Preferred Term (n [%])[a]	White (n=19)	All Other (n=9)	White (n=3)	All Other (n=2)	White (n=51)	All Other (n=40)	White (n=73)	All Other (n=51)
Patients With at Least One SAE	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (3.9)	0 (0.0)	3 (4.1)	0 (0.0)
Cardiac Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.9)	0 (0.0)	2 (2.7)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Cardiac Arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Low CO Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (2.0)	0 (0.0)	2 (2.7)	0 (0.0)
ECG ST Segment Elevation	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Oxygen Saturation Decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Respiratory, Thoracic, and Mediastinal Disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
PH	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (1.4)	0 (0.0)
Vascular Disorders	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)
Hypotension	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	0 (0.0)

[a] System organ classes and preferred terms are coded using the MedDRA dictionary. System organ classes and preferred terms are listed in descending order of frequency for the Overall column. A patient with multiple occurrences of an AE is counted only once in the AE category.

Source: Section 14.3.1, Table 9.4 and Appendix 16.2.7

12.3.1.3. Other Significant Adverse Events

Two patients withdrew from treatment due to AEs (Table 35). Treatment was stopped in one patient due to decreased O_2 saturation (possibly related to study treatment) and in a second patient due to hypotension and ST segment elevation (probably related to study treatment).

Table 33: Adverse Events Leading to Withdrawal From Treatment (Safety)

Adverse Event	Number of Patients (%) (n=124)
Cardiovascular	1 (0.8)
Hypotension and ST Segment Elevation	1 (0.8)
Investigations	1 (0.8)
O_2 Saturation Decreased	1 (0.8)

Source: Appendix 16.2.7

12.3.2. Narratives of Deaths, Other Serious Adverse Events, and Certain Other Significant Adverse Events

12.3.2.1. Deaths

Patient 04-001 ([redacted]S1000863) (Hypotension, cardiac arrest) was a 2-year, 6-month-old male. As a neonate, the patient had coarctation of the aorta requiring surgery by means of the Waldhausen technique. He was followed 5 months later with percutaneous angioplasty for recoarctation, with good hemodynamic results. Two years later, the patient suffered severe symptoms of low CO and was diagnosed with severe mitral stenosis. Surgical implantation of a mechanical mitral prosthetic valve had no beneficial effect, and the patient experienced severe left ventricular dysfunction in the postoperative period. The patient was transferred for evaluation of pulmonary resistances and the conditions for heart transplantation, and was entered into the present study. The patient received NO 80 ppm for 79 minutes. Thirty minutes after withdrawal of study medication, the patient suffered hypotension, bradycardia, hypoxemia, and cardiac arrest. A cardiac massage and dobutamine infusion were initiated; the patient recovered the normal rhythm and normal tension values in 15 minutes. He was transferred to the intensive care unit. Treatment with dobutamine, sildenafil, and sedation was maintained during the next 72 hours. Catheterization was repeated the next day to reevaluate the pulmonary resistances; NO was administered with a hospital device, outside the study protocol, with an oral loading dose of sildenafil. There was no response in pulmonary pressure, and the patient died 8 hours after the procedure in the intensive care unit with refractory hypotension. During and after the study, the patient received the following concomitant medications: sevoflurane, rocuronium bromide, fentanyl citrate, dobutamine, milrinone, sildenafil, ranitidine, cefazolin, acetaminophen, enoxaparin, and midazolam. The investigator deemed this event to be unrelated to study medication.

Patient 04-008 ([redacted]S10000682) (Pulmonary Hypertension, Hypotension, Hypoxemia, Bradycardia) was a 4-year-old male with a history of congenital heart disease, increased right ventricular pressure, ventricular septal defect repair, pulmonary artery stenosis, transposition of the great vessels, balloon atrial septostomy, pulmonary hypertension, Eisenmenger's syndrome, and dilatation of the right ventricle and right-to-left shunt across the small residual ventricular septal defect. He underwent a cardiac catheterization for pulmonary artery stenosis. During the procedure a very high pressure was found in both pulmonary branches with a transpulmonary gradient increase. The patient received NO 80 ppm for a total of 70 minutes. Between the first and second segment of the protocol (O_2 100% and NO 80 ppm) the patient was accidentally extubated and the investigator delayed the collection of data 40 minutes until the child recovered the hemodynamic and gasometric stability. During the last phase of the protocol, while receiving NO alone, the patient experienced severe hypotension with hypoxemia and bradycardia. The protocol was discontinued, and the patient was treated with dobutamine and 100% O_2. There was an initial improvement in O_2 saturation; arterial tension and sinus rhythm recovery were obtained. The patient was transferred to the intensive care unit. During the following hours, he suffered a severe deterioration with PH and right ventricular failure. Despite administration of 100% O_2, NO at 20 ppm, and other therapies (rocuronium bromide, atropine, dobutamine, milrinone, dopamine, vecuronium, epinephrine, sildenafil, fentanyl, ceftazidime, teicoplanin, furosemide, NO, and hyperventilation), the patient expired the next day after atrial fibrillation.

Performed on Day 1, echocardiography results showed increased right ventricular pressure in the last month; chest x-ray results showed no pleural effusion, and laboratory tests showed the following values: Hgb 12 g/dL; platelets 301,000/μL; leukocytes 9.1 x $10^3/mm^3$; neutrophils 60.5%; glucose 272 mg/dL; urea 39 mg/dL; calcium 9.2 mg/dL; alanine aminotransferase 16 U/L; and aspartate aminotransferase 19 U/L. The investigator deemed this event to have a probable relation to the study drug.

Patient 05-002 ([redacted]S1000062) (Hypoxia/Bradycardia) was a 4-month-old female with a history of congenital heart disease (atrioventricular septal defect) and secondary pulmonary hypertension. One and a half hours after the start of catheterization, the posterior aortic cusp was accidentally perforated, resulting in moderate aortic regurgitation. When the procedure was completed, the patient was extubated and began to breathe on her own. Post-procedure testing showed the following values: platelets 269,000/μL; pH 7.41; Hgb 10.2 g/dL; erythrocytes 3.00 x $10^6/\mu L$; and hematocrit 31.8%. Two hours after the procedure was completed, the patient suffered oxygen desaturation and severe bradycardia. She required cardiopulmonary resuscitation, which was unsuccessful. Forty minutes later the patient expired. The patient received the following additional concomitant medications: atropine, sevoflurane, fentanyl citrate, and thiopental sodium. Postmortem examination showed hepatization of the lungs, cardiomegaly in the presence of atrioventricular septal defect, severe atrioventricular valve insufficiency, and iatrogenic perforation of the posterior aortic cusp. The investigator judged that subjecting the patient to 100% O_2 for 10 minutes (the first dose) followed by nitric oxide at 80 ppm and 100% O_2 for 10 minutes (the second dose) significantly unbalanced her cardiac output, which led in turn to a severe drop in PVR (from 708 to 88 mm Hg), massive blood overflow to the lungs, and a severe reduction in CO. The investigator, noting that this patient had structural cardiopathy, atrioventricular septal defect, severe pulmonary vascular hypertension, severe atrioventricular valve insufficiency, and moderate aortic regurgitation, judged that "a confluence of different factors" had caused this child's progressive deterioration and death and deemed this event to be unrelated to study medication. However, the medical monitor deemed this event to be possibly related to study medication.

12.3.2.2. Nonfatal Serious Adverse Events * ADD statement: re:Protocol language re: SAE collection up to 12 hours (p.38;Sec.10.4.2) not collected on CRF or Clin database but collected in pharmacovigilance database

Patient 02-002 ([redacted]S1000794) (Pulmonary edema) was a 10-month-old male with a history of mitral regurgitation and PH. After the cardiac catheterization, the patient experienced pulmonary edema, probably due to the administration of contrast for angiography in the setting of severe mitral regurgitation with pulmonary hypertension. The patient was managed in the intensive care unit with mechanical ventilation and improved within 48 hours. He was discharged to the floor after 3 days. The patient received the following additional concomitant medications on the day of therapy: heparin, atracurium besylate, cefamandole, and alfentanil hydrochloride. The investigator deemed this event to be unrelated to study medication.

Patient 07-003 ([redacted]S1000682) (Cardiac arrest) was a 14-year-old female with a history of primary pulmonary hypertension, epilepsy, asthma, von Willebrand's disease, and Factor V Leiden deficiency. Eighty minutes post cardiac catheterization, the patient required

cardiopulmonary resuscitation for 90 seconds due to bradycardia down to 42 beats per minute. She required high ventilatory pressure and was treated with NO and transferred to the pediatric intensive care unit, where she experienced three more episodes of hypertension and required short boluses of adrenaline and cardiopulmonary resuscitation overnight. Thirteen days after the event, she was successfully weaned off nitric oxide, and was extubated on the following day. She was diagnosed with von Willebrand's disease and factor V Leiden deficiency. Five weeks after the event, the patient was transferred to another facility for a full assessment of her pulmonary hypertension. She has remained stable with no major concerns, and has recovered almost completely (psychologically and physically) from her cardiac arrest. Seven weeks after the event, she was discharged to home. Confirmatory laboratory tests included electrocardiogram, echocardiogram, electroencephalogram, and an angiogram. The electrocardiogram showed normal sinus rhythm with signs of right ventricular hypertrophy and repolarization abnormalities. The echocardiogram showed normal atrioventricular and ventricular arterial connections; the left ventricle had normal dimensions and function and a shortening fraction of 39.5%; the right ventricle appeared to be slightly dilated and mildly hypertrophic but had preserved its function, although the contractility was sluggish. The electroencephalogram was within normal limits, and the angiogram shown mild enlargement of central pulmonary arteries. On the day that study therapy was administered, the patient received the following additional concomitant medications: vecuronium bromide, propofol, ondansetron, paracetamol, and sodium chloride compound injection. Additionally, the patient received concomitant therapy with the following medicinal products from an unknown starting date until the present date: epoprostenol sodium, sildenafil, lamotrigine, and warfarin. The investigator deemed this event to have a possible relation to the study drug.

Patient 17-001 ([redacted]S1000083) (Hypoxia) was an 8-year-old male with a history of pulmonary hypertension, asthma, adrenal insufficiency, and aorticopulmonary window. The patient completed the study without an adverse event. The physician decided to address the recent history of hemoptysis. An ascending aorta/aortic arch angiogram was performed. No large collaterals were identified off the aortic arch or right or left mammary arteries. In the mid-thoracic and descending aorta, some large anteroposterior and several tiny anteroposterior collaterals were found. Coil closure of the large anteroposterior collaterals was performed. The patient was stable, and sheaths were removed with good hemostasis. Approximately 3.5 hours later, the patient complained of right chest pain (10 on a scale of 10). Heart rate was 99 beats per minute, respiratory rate was 28, and temperature was 37.1°C. Oxygen saturation was 71%. He was treated with acetaminophen for pain and chest pain was reported as 2 on a scale of 10. His O_2 saturation continued to decrease (64-68%) despite oxygen at 2 L via nasal cannula. He was placed on a nonrebreather mask. He became cyanotic, with stridor, and nausea with emesis. He was given ondansetron hydrochloride and intravenous fluids. The patient was transferred to the pediatric intensive care unit for closer monitoring. Stress steroids were given at 19 mg every 6 hours, sildenafil 5 mg every 6 hours, ondansetron as needed, and oxygen to maintain O_2 saturation level >70%. The patient was also receiving ongoing treatment with the following additional concomitant medications: digoxin, bosentan, esomeprazole magnesium, fluticasone propionate, hydrocortisone acetate, montelukast sodium, and ipratropium bromide. The patient was discharged from the hospital in good health 2 days after the event. The investigator deemed the events to be possibly related to a combination of inadequate steroids for adrenal insufficiency and the use of intravenous dye. His pain was judged likely to be related to the anteroposterior

coil placement. The investigator deemed the hypoxia to be unlikely to be related to study medication.

12.3.2.3. Discontinuations Due to Adverse Events

Patient 01-020 (Desaturation during NO administration) was a 1-year-old female with a diagnosis of CHD with pulmonary hypertension and a history of a repaired ventricular septal defect. Seven minutes after initiation of the administration of the third dose of NO, the patient experienced mild systemic desaturation (35%). The protocol was discontinued and the event resolved after 2 minutes. During the study period, the patient received concomitant treatment with intravenous midazolam and nalbuphine hydrochloride. The investigator deemed this event to have a possible relation to the study drug.

Patient 04-003 ([redacted]1000160) (Hypotension, Electrocardiogram ST segment elevation) was an 8.4-year-old female with a history of cardiac valvuloplasty in the neonatal period, aortic stenosis, moderate aortic regurgitation, cardiomyopathy, and pulmonary hypertension. After 4 minutes on NO with 100% O_2 withdrawal, the patient experienced severe systemic hypotension with the same pulmonary pressure and elevation of ST segment in the electrocardiogram. The protocol was discontinued and treatment with 100% O_2 and a dobutamine infusion was initiated. The patient recovered normal pressure in 20 minutes. The patient was intubated and transferred to the pediatric intensive care unit where she was extubated after 8 hours without complications. The patient received the following additional concomitant medications: rocuronium bromide, fentanyl citrate, midazolam, and sevoflurane. The investigator deemed this event to have a probable relation to the study drug.

12.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events [redacted]

There was one death considered probably related to two AEs (hypotension and ST segment elevation, both considered to be probably related to study treatment) and two other SAEs in one other patient (low CO syndrome and pulmonary hypertension, both probably related to study treatment) that were not fatal. Treatment was stopped in two patients as a result of AEs. The first patient was the above-described individual who died and the second experienced decreased O_2 saturation considered as possibly related to study drug. Another patient suffered oxygen desaturation and severe bradycardia two hours postprocedure, followed by cardiac arrest and death. Although the investigator cited the patient's numerous underlying cardiovascular conditions in deeming the event unrelated to study medication, the medical monitor considered it possibly related.

12.4. Clinical Laboratory Evaluation

No clinical laboratory evaluation was carried out as part of the safety evaluation for this study.

12.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

Table 34: Vital signs - HR Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
HR (beats/minute)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	105.8	105.7	106.6
SD	28.84	30.33	30.72
Median	104.5	102.0	103.5
Minimum, maximum	51.0, 168.0	39.0, 168.0	51.0, 180.0
Post-treatment			
Mean	104.1	102.8	105.9
SD	33.02	30.76	31.57
Median	97.5	97.0	100.0
Minimum, maximum	45.0, 192.0	53.0, 165.0	46.0, 179.0
Change From Baseline			
Mean	-1.7	-2.8	-0.8
SD	13.69	11.35	9.47
Median	-3.0	-3.0	0.0
Minimum, maximum	-38.0, 41.0	-33.0, 38.0	-36.0, 28.0
p-value[a]	0.173	0.007	0.382

[a] p-value from a t-test. Only patients with baseline and post-treatment data are included in the analysis.
Source: Section 14.3.4, Table 11.1.1 and Appendix 16.2.9

NO plus O_2 and O_2 slightly increased SAP in both the intent-to-treat (Table 37) and per-protocol populations. The increase for NO plus O_2 was statistically significant in the per-protocol population (2.9 mm Hg, p=0.028). Treatment with NO slightly increased SAP in the intent-to-treat population and decreased it in the per-protocol population.

Table 35: Vital signs - SAP Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
SAP (mm Hg)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	85.4	85.7	86.7
SD	15.03	15.24	15.17
Median	85.0	85.0	85.5
Minimum, maximum	51.0, 132.0	51.0, 132.0	51.0, 126.0
Post-treatment			
Mean	87.4	87.5	86.1
SD	16.63	17.17	16.90
Median	87.0	88.0	84.0
Minimum, maximum	45.0, 136.0	48.0, 130.0	32.0, 134.0
Change From Baseline			
Mean	2.0	1.8	-0.6
SD	11.42	10.56	8.19
Median	1.0	2.0	1.0
Minimum, maximum	-36.0, 49.0	-32.0, 43.0	-25.0, 17.0
p-value[a]	0.057	0.068	0.430

[a] p-value from a t-test. Only patients with baseline and post-treatment data are included in the analysis.
Source: Section 14.3.4, Table 11.2.1 and Appendix 16.2.9

Table 36: Vital signs - DAP Change From Baseline By Treatment (Intent-to-Treat)

	Treatment		
DAP (mm Hg)	**NO Plus O_2 (n=124)**	**O_2 (n=121)**	**NO (n=120)**
Baseline (room air)			
Mean	47.3	48.0	48.6
SD	12.19	11.90	12.86
Median	47.0	48.0	49.0
Minimum, maximum	23.0, 83.0	25.0, 83.0	19.0, 86.0
Post-treatment			
Mean	48.8	49.9	47.8
SD	12.61	12.21	13.06
Median	50.0	50.0	47.0
Minimum, maximum	24.0, 92.0	24.0, 90.0	22.0, 84.0
Change From Baseline			
Mean	1.4	1.8	-0.8
SD	8.63	7.65	6.56
Median	0.5	2.0	0.0
Minimum, maximum	-23.0, 28.0	-28.0, 21.0	-25.0, 15.0
p-value[a]	0.071	0.009	0.184

[a] p-value from a t-test. Only patients with baseline and post-treatment data are included in the analysis.
Source: Section 14.3.4, Table 11.3.1 and Appendix 16.2.9

12.6. Safety Conclusions

Study treatments had slight and non-clinically significant effects on vital signs, including HR, SAP, and DAP.

There was one death considered related to two AEs (hypotension and ST segment elevation, both considered to be probably related to study treatment) and two other serious AEs in one other patient (low CO output syndrome and pulmonary hypertension, both probably related to study treatment) that were serious, but not fatal. Treatment was stopped in two patients as a result of AEs. The first patient was the above-described individual who died and the second experienced decreased O_2 saturation considered as possibly related to study drug. Another patient suffered oxygen desaturation and severe bradycardia two hours postprocedure, followed by cardiac arrest and death. Although the investigator cited the patient's numerous underlying cardiovascular conditions in deeming the event unrelated to study medication, the medical monitor considered it possibly related.

All treatments were well tolerated and seven patients experienced AEs during this study. These included cardiac arrest, bradycardia, low CO syndrome, elevated ST segment on the ECG, decreased O_2 saturation, hypotension, mouth hemorrhage, and PH. The numbers of patients and events are too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender, or race.

A total of four patients had AEs were related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH, and hypotension.

All but two AEs were mild or moderate in intensity and resolved.

Serious adverse events were collected from the start of study treatment until hospital discharge or 24 hours, whichever occurred sooner. Six SAEs were reported. Three of these were fatal SAEs, and 3 were nonfatal. Two of the three fatal SAEs were considered related to therapy, as were 2 of three nonfatal SAEs. The numbers of patients and events are too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender, or race.

Treatment was stopped in two patients as a result of AEs. The first patient was the above-described individual who died and the second experienced decreased O_2 saturation considered as possibly related to study drug.

We note that two patients developed signs of pulmonary edema.

The overall numbers of SAEs and fatal SAEs are within the range of expected for patients with this degree of cardiopulmonary disease. The overall rate is 6/124 (4.8%). This is comparable to the rate of 6% recently reported by Taylor et al in a very similar cohort of patients.[15]

13. DISCUSSION AND OVERALL CONCLUSIONS

The results from this study showed that NO plus O_2 resulted in a significantly higher pulmonary vasoreactivity response rate (25.7%) versus O_2 alone (14.7%) ($p = 0.019$). In addition, 17.4% of patients responded only to NO plus O_2 versus 6.4% who responded to O_2 only. The results for the per-protocol population generally supported those for the intent-to-treat population, but the population was smaller and the statistical power was lower due to the high number of protocol violations.

The present findings are consistent with the conclusion that NO plus O_2 is more effective than O_2 alone when used as a pulmonary vasodilator. These results are consistent with those from a smaller study of 46 patients with a broad spectrum of pediatric cardiac disease, including atrial septal defect, complete atrioventricular canal, Shone's syndrome, patent ductus arteriosus, truncus arteriosus, and other conditions. In this study, combining 100% O_2 and 80 ppm NO produced a response of ≥ 20% in PVR in 88% of patients versus 64% for O_2 alone ($p = 0.01$).[11] Other prior studies have also reported differences in responses to NO, O_2, and/or the combination of these treatments.[16-18]

Individually, NO and O_2 produced significant and comparable selective pulmonary vasodilation, and they may do so via different mechanisms. It has been demonstrated that NO produces vasorelaxation via a guanosine monophosphate-mediated pathway,[19] but the mechanisms by which O_2 decreases PVR are not known.[11] The observation in the present and a prior study[11] that some patients responded to one agent, but not the other, suggests that the mechanisms underlying NO- and O_2-induced vasorelaxation may be at least somewhat different.

The ability of NO plus O_2 to detect a higher percentage of patients than O_2 alone is clinically important. Patients who respond to pulmonary vasodilator testing have better outcomes when undergoing repair of congenital heart defects.[20-22] The response to acute vasodilator testing in patients with primary PH is an important marker for survival[23] and may also identify patients suitable for long-term medical therapy.[24, 25]

All treatments delivered in this study were well tolerated and only seven patients experienced AEs. All but two AEs were mild or moderate in intensity and resolved. There were two severe AEs (low CO syndrome and hypertension, experienced by a single patient) that resulted in death. Among the 124 patients who received treatment in this study, six suffered an SAE during or immediately following the procedure, an overall rate of 4.8%. This is within the expected range of SAEs for patients with this degree of cardiopulmonary disease. Results from a series of 75 pediatric patients with PH undergoing cardiac catheterization under anesthesia indicated that resuscitation or death occurred in 6% of patients.[15] Caution is warranted when using NO with oxygen in patients susceptible to pulmonary edema, i.e., patients with significantly elevated PCWP or other signs of poor LV function.

All treatments appear to be highly selective for the pulmonary vasculature. In each treatment period, the ratio of PAPm to MAP (and likewise the ratio of PRVI to SVRI) decreases with treatment, indicating a greater decrease in the pulmonary pressure than in the systemic pressures.

This is consistent with the direct delivery of therapy to the lungs. Although there is no internal control for pulmonary selectivity in this study, we may compare the change in the ratio of PAPm/MAP with that seen with systemic therapy with prostacyclin or sildenafil. With these therapies, that ratio is typically unchanged or increased.[26-29]

We note that this study randomized only the first treatment assignment; the second treatment period was the combination treatment, and the final treatment was the individual therapy not given in the first period. This was done for clinical reasons; requiring a third washout and baseline period would have made the procedure unacceptably long, subjecting these patients to additional risk. However, without a completely randomized treatment sequence and separate baseline periods, we cannot completely exclude an interaction of treatment with period. We note that the baseline PVRI was similar in baseline period 1 and baseline period 2. The results appear to be quite robust. The results are consistent with the known mechanism of action, and the study results appear to be fully consistent with both internal and previous reports.

In conclusion, the present results indicate that combination testing with NO plus O_2 provides additional pulmonary vasodilation, can be safely delivered to patients during diagnostic cardiac catheterization, and can rapidly identify patients with pulmonary vasoreactivity who may not be recognized with delivery of O_2 alone.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

None

14.1. Demographic Data Summary Figures and Tables

14.2. Efficacy Data Summary Figures and Tables

14.3. Safety Data Summary Figures and Tables

14.3.1. Displays of Adverse Events

14.3.2. Listings of Deaths, Other Serious and Significant Adverse Events

14.3.3. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Narrative Category: <Death, Discontinuation Due to an Adverse Event, SAE>

Identification:

Protocol No.	<insert>
Patient No.	<insert>
Patient Initials	<insert>
Patient DOB	<insert>
Adverse Event	
Treatment	
Relationship to Drug	

Demographics:

Age (at time of event)

Gender

Race

Dosing:

Dose

Route

Duration (until event)

Regimen

Medical History:

Relevant Prior Illnesses

Relevant Prior Medications

Current Medical Status:

Clinical Condition

Disease Being Treated

Relevant Concomitant Illnesses

Relevant Concomitant Medications

Relevant Laboratory Measurements

Description of Event:

14.3.4. Abnormal Laboratory Value Listing

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INOmax® (nitric oxide) for inhalation
100 and 800 ppm (parts per million)

DESCRIPTION
INOmax (nitric oxide gas) is a drug administered by inhalation. Nitric oxide, the active substance in INOmax, is a pulmonary vasodilator. INOmax is a gaseous blend of nitric oxide and nitrogen (0.08% and 99.92%, respectively for 800 ppm; 0.01% and 99.99%, respectively for 100 ppm). INOmax is supplied in aluminum cylinders as a compressed gas under high pressure (2000 pounds per square inch gauge [psig]).

The structural formula of nitric oxide (NO) is shown below:

$$\cdot\dot{\ddot{N}} = \ddot{O}:$$

CLINICAL PHARMACOLOGY
Nitric oxide is a compound produced by many cells of the body. It relaxes vascular smooth muscle by binding to the heme moiety of cytosolic guanylate cyclase, activating guanylate cyclase and increasing intracellular levels of cyclic guanosine 3',5'-monophosphate, which then leads to vasodilation. When inhaled, nitric oxide produces pulmonary vasodilation.

INOmax appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios.

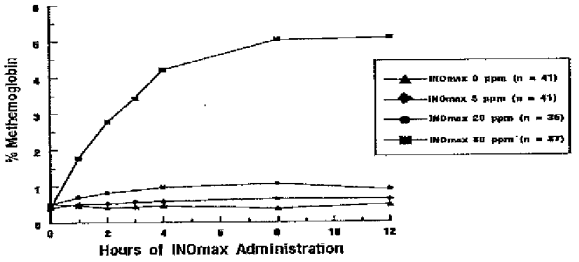
Effects on Pulmonary Vascular Tone in PPHN
Persistent pulmonary hypertension of the newborn (PPHN) occurs as a primary developmental defect or as a condition secondary to other diseases such as meconium aspiration syndrome (MAS), pneumonia, sepsis, hyaline membrane disease, congenital diaphragmatic hernia (CDH), and pulmonary hypoplasia. In these states, pulmonary vascular resistance (PVR) is high, which results in hypoxemia secondary to right-to-left shunting of blood through the patent ductus arteriosus and foramen ovale. In neonates with PPHN, INOmax improves oxygenation (as indicated by significant increases in PaO_2).

PHARMACOKINETICS
The pharmacokinetics of nitric oxide has been studied in adults.

Uptake and Distribution
Nitric oxide is absorbed systemically after inhalation. Most of it traverses the pulmonary capillary bed where it combines with hemoglobin that is 60% to 100% oxygen-saturated. At this level of oxygen saturation, nitric oxide combines predominantly with oxyhemoglobin to produce methemoglobin and nitrate. At low oxygen saturation, nitric oxide can combine with deoxyhemoglobin to transiently form nitrosylhemoglobin, which is converted to nitrogen oxides and methemoglobin upon exposure to oxygen. Within the pulmonary system, nitric oxide can combine with oxygen and water to produce nitrogen dioxide and nitrite, respectively, which interact with oxyhemoglobin to produce methemoglobin and nitrate. Thus, the end products of nitric oxide that enter the systemic circulation are predominantly methemoglobin and nitrate.

Metabolism
Methemoglobin disposition has been investigated as a function of time and nitric oxide exposure concentration in neonates with respiratory failure. The methemoglobin (MetHb) concentration-time profiles during the first 12 hours of exposure to 0, 5, 20, and 80 ppm INOmax are shown in Figure 1.

Figure 1
Methemoglobin Concentration - Time Profiles
Neonates Inhaling 0, 5, 20 or 80 ppm INOmax



Methemoglobin concentrations increased during the first 8 hours of nitric oxide exposure. The mean methemoglobin level remained below 1% in the placebo group and in the 5 ppm and 20 ppm INOmax groups, but reached approximately 5% in the 80 ppm INOmax group. Methemoglobin levels >7% were attained only in patients receiving 80 ppm, where they comprised 35% of the group. The average time to reach peak methemoglobin was 10 ± 9 (SD) hours (median, 8 hours) in these 13 patients; but one patient did not exceed 7% until 40 hours.

Elimination
Nitrate has been identified as the predominant nitric oxide metabolite excreted in the urine, accounting for >70% of the nitric oxide dose inhaled. Nitrate is cleared from the plasma by the kidney at rates approaching the rate of glomerular filtration.

CLINICAL TRIALS
The efficacy of INOmax has been investigated in term and near-term newborns with hypoxic respiratory failure resulting from a variety of etiologies. Inhalation of INOmax reduces the oxygenation index (OI= mean airway pressure in cm H_2O x fraction of inspired oxygen concentration [FIO_2] x 100 divided by systemic arterial concentration in mm Hg [PaO_2]) and increases PaO_2 (See CLINICAL PHARMACOLOGY).

NINOS study
The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether inhaled nitric oxide would reduce the occurrence of death and/or initiation of extracorporeal membrane oxygenation (ECMO) in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O / mm Hg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm nitric oxide for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = >20 mm Hg, partial = 10-20 mm Hg, no response = <10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm nitric oxide or control gas. The primary results from the NINOS study are presented in Table 1.

Table 1
Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*,†	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

Although the incidence of death by 120 days of age was similar in both groups (NO, 14%; control, 17%), significantly fewer infants in the nitric oxide group required ECMO compared with controls (39% vs. 55%, p = 0.014). The combined incidence of death and/or initiation of ECMO showed a significant advantage for the nitric oxide treated group (46% vs. 64%, p = 0.006). The nitric oxide group also had significantly greater increases in PaO_2 and greater decreases in the OI and the alveolar-arterial oxygen gradient than the control group (p<0.001 for all parameters). Significantly more patients had at least a partial response to the initial administration of study drug in the nitric oxide group (66%) than the control group (26%, p<0.001). Of the 125 infants who did not respond to 20 ppm nitric oxide or control, similar percentages of NO-treated (18%) and control (20%) patients had at least a partial response to 80 ppm nitric oxide for inhalation or control drug, suggesting a lack of additional benefit for the higher dose of nitric oxide. No infant had study drug discontinued for toxicity. Inhaled nitric oxide had no detectable effect on mortality. The adverse events collected in the NINOS trial occurred at similar incidence rates in both treatment groups (See ADVERSE REACTIONS). Follow-up exams were performed at 18–24 months for the infants enrolled in this trial. In the infants with available follow-up, the two treatment groups were similar with respect to their mental, motor, audiologic, or neurologic evaluations.

CINRGI study
This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax would reduce the receipt of ECMO in these patients. Hypoxic respiratory failure was caused by MAS (35%), idiopathic PPHN (30%), pneumonia/sepsis (24%), or RDS (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean OI of 44 cm H_2O / mm Hg were randomly assigned to receive either 20 ppm INOmax (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients who exhibited a PaO_2 >60 mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax or placebo. The primary results from the CINRGI study are presented in Table 2.

Table 2
Summary of Clinical Results from CINRGI Study

	Placebo	INOmax	P value
ECMO*,†	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

* Extracorporeal membrane oxygenation
† ECMO was the primary end point of this study

Significantly fewer neonates in the INOmax group required ECMO compared to the control group (31% vs. 57%, p<0.001). While the number of deaths were similar in both groups (INOmax, 3%; placebo, 6%), the combined incidence of death and/or receipt of ECMO was decreased in the INOmax group (33% vs. 58%, p<0.001).

In addition, the INOmax group had significantly improved oxygenation as measured by PaO_2, OI, and alveolar-arterial gradient (p<0.001 for all parameters). Of the 97 patients treated with INOmax, 2 (2%) were withdrawn from study drug due to methemoglobin levels >4%. The frequency and number of adverse events reported were similar in the two study groups (See ADVERSE REACTIONS).

ARDS study
In a randomized, double-blind, parallel, multicenter study, 385 patients with adult respiratory distress syndrome (ARDS) associated with pneumonia (46%), surgery (33%), multiple trauma (26%), aspiration (23%), pulmonary contusion (18%), and other causes, with PaO_2/FIO_2 <250 mm Hg despite optimal oxygenation and ventilation, received placebo (n=193) or INOmax (n=192), 5 ppm, for 4 hours to 28 days or until weaned because of improvements in oxygenation. Despite acute improvements in oxygenation, there was no effect of INOmax on the primary endpoint of days alive and off ventilator support. These results were consistent with outcome data from a smaller dose ranging study of nitric oxide (1.25 to 80 ppm). INOmax is not indicated for use in ARDS.

INDICATIONS
INOmax, in conjunction with ventilatory support and other appropriate agents, is indicated for the treatment of term and near-term (>34 weeks) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, where it improves oxygenation and reduces the need for extracorporeal membrane oxygenation.

CONTRAINDICATIONS
INOmax should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

PRECAUTIONS
Rebound
Abrupt discontinuation of INOmax may lead to worsening oxygenation and increasing pulmonary artery pressure.

Methemoglobinemia
Methemoglobinemia increases with the dose of nitric oxide. In the clinical trials, maximum methemoglobin levels usually were reached approximately 8 hours after initiation of inhalation, although methemoglobin levels have peaked as late as 40 hours following initiation of INOmax therapy. In one study, 13 of 37 (35%) of neonates treated with INOmax 80 ppm had methemoglobin levels exceeding 7%. Following discontinuation or reduction of nitric oxide the methemoglobin levels returned to baseline over a period of hours.

Elevated NO_2 Levels
In one study, NO_2 levels were <0.5 ppm when neonates were treated with placebo, 5 ppm, and 20 ppm nitric oxide over the first 48 hours. The 80 ppm group had a mean peak NO_2 level of 2.6 ppm.

Drug Interactions
No formal drug-interaction studies have been performed, and a clinically significant interaction with other medications used in the treatment of hypoxic respiratory failure cannot be excluded based on the available data. INOmax has been administered with tolazoline, dopamine, dobutamine, steroids, surfactant, and high-frequency ventilation. Although there are no study data to evaluate the possibility, nitric oxide donor compounds, including sodium nitroprusside and nitroglycerin, may have an additive effect with INOmax on the risk of developing methemoglobinemia. An association between prilocaine and an increased risk of methemoglobinemia, particularly in infants, has specifically been described in a literature case report. This risk is present whether the drugs are administered as oral, parenteral, or topical formulations.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No evidence of a carcinogenic effect was apparent, at inhalation exposures up to the recommended dose (20 ppm), in rats for 20 hr/day for up to two years. Higher exposures have not been investigated.

Nitric oxide has demonstrated genotoxicity in Salmonella (Ames Test), human lymphocytes, and after *in vivo* exposure in rats. There are no animal or human studies to evaluate nitric oxide for effects on fertility.

Pregnancy: Category C
Animal reproduction studies have not been conducted with INOmax. It is not known if INOmax can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. INOmax is not intended for adults.

Nursing Mothers
Nitric oxide is not indicated for use in the adult population, including nursing mothers. It is not known whether nitric oxide is excreted in human milk.

Pediatric Use
Nitric oxide for inhalation has been studied in a neonatal population (up to 14 days of age). No information about its effectiveness in other age populations is available.

ADVERSE REACTIONS
Controlled studies have included 325 patients on INOmax doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax, a result adequate to exclude INOmax mortality being more than 40% worse than placebo.

In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax and placebo-treated groups.

From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax and 212 patients who received placebo. Among these patients, there was no evidence of an adverse effect of treatment on the need for rehospitalization, special medical services, pulmonary disease, or neurological sequelae.

In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, periventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

The table below shows adverse events with an incidence of at least 5% on INOmax in the CINRGI study, and that were more common on INOmax than on placebo.

ADVERSE EVENTS IN THE CINRGI TRIAL

Adverse Event	Placebo (n=89)	Inhaled NO (n=97)
Hypotension	9 *(10%)*	13 *(13%)*
Withdrawal	9 *(10%)*	12 *(12%)*
Atelectasis	8 *(9%)*	9 *(9%)*
Hematuria	5 *(6%)*	8 *(8%)*
Hyperglycemia	6 *(7%)*	8 *(8%)*
Sepsis	2 *(2%)*	7 *(7%)*
Infection	3 *(3%)*	6 *(6%)*
Stridor	3 *(3%)*	5 *(5%)*
Cellulitis	0 *(0%)*	5 *(5%)*

OVERDOSAGE
Overdosage with INOmax will be manifest by elevations in methemoglobin and NO_2. Elevated NO_2 may cause acute lung injury. Elevations in methemoglobinemia reduce the oxygen delivery capacity of the circulation. In clinical studies, NO_2 levels >3 ppm or methemoglobin levels >7% were treated by reducing the dose of, or discontinuing, INOmax.

Methemoglobinemia that does not resolve after reduction or discontinuation of therapy can be treated with intravenous vitamin C, intravenous methylene blue, or blood transfusion, based upon the clinical situation.

POST-MARKETING EXPERIENCE
The following adverse events have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

DOSAGE AND ADMINISTRATION
Dosage
The recommended dose of INOmax is 20 ppm. Treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax therapy.

An initial dose of 20 ppm was used in the NINOS and CINRGI trials. In CINRGI, patients whose oxygenation improved with 20 ppm were dose-reduced to 5 ppm as tolerated at the end of 4 hours of treatment. In the NINOS trial, patients whose oxygenation failed to improve on 20 ppm could be increased to 80 ppm, but those patients did not then improve on the higher dose. As the risk of methemoglobinemia and elevated NO_2 levels increases significantly when INOmax is administered at doses >20 ppm, doses above this level ordinarily should not be used.

Administration
Additional therapies should be used to maximize oxygen delivery. In patients with collapsed alveoli, additional therapies might include surfactant and high-frequency oscillatory ventilation.

The safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. Different dose regimens for nitric oxide were used in the clinical studies (see CLINICAL TRIALS).

INOmax should be administered with monitoring for PaO_2, methemoglobin, and NO_2.

The nitric oxide delivery systems used in the clinical trials provided operator-determined concentrations of nitric oxide in the breathing gas, and the concentration was constant throughout the respiratory cycle. INOmax must be delivered through a system with these characteristics and which does not cause generation of excessive inhaled nitrogen dioxide. The INOvent® system and other systems meeting these criteria were used in the clinical trials. In the ventilated neonate, precise monitoring of inspired nitric oxide and NO_2 should be instituted, using a properly calibrated analysis device with alarms. The system should be calibrated using a precisely defined calibration mixture of nitric oxide and nitrogen dioxide, such as INOcal®. Sample gas for analysis should be drawn before the Y-piece, proximal to the patient. Oxygen levels should also be measured.

In the event of a system failure or a wall-outlet power failure, a backup battery power supply and reserve nitric oxide delivery system should be available.

The INOmax dose should not be discontinued abruptly as it may result in an increase in pulmonary artery pressure (PAP) and/or worsening of blood oxygenation (PaO_2). Deterioration in oxygenation and elevation in PAP may also occur in children with no apparent response to INOmax. Discontinue/wean cautiously.

HOW SUPPLIED
INOmax (nitric oxide) is available in the following sizes:

Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-002-01)

Size D Portable aluminum cylinders containing 353 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 344 liters) (NDC 64693-001-01)

Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 800 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-002-02)

Size 88 Aluminum cylinders containing 1963 liters at STP of nitric oxide gas in 100 ppm concentration in nitrogen (delivered volume 1918 liters) (NDC 64693-001-02)

Store at 25°C (77°F) with excursions permitted between 15–30°C (59–86°F) [see USP Controlled Room Temperature].

Occupational Exposure
The exposure limit set by the Occupational Safety and Health Administration (OSHA) for nitric oxide is 25 ppm, and for NO_2 the limit is 5 ppm.

CAUTION
Federal law prohibits dispensing without a prescription.

INO Therapeutics
6 Route 173 West
Clinton, NJ 08809
USA

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The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 14/454,373	Applicant(s) BALDASSARRE, JAMES S.	
	Examiner ERNST V. ARNOLD	Art Unit 1613	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTHS FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims*

5)☒ Claim(s) *31-60* is/are pending in the application.

5a) Of the above claim(s) _____ is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *31-60* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a)☐ All b)☐ Some** c)☐ None of the:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

** See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☒ Information Disclosure Statement(s) (PTO/SB/08a and/or PTO/SB/08b) Paper No(s)/Mail Date *8/7/14, 8/8/14, 8/13/14, 8/14/14, 8/15/14 and 8/25/14* .

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Claims 1-30 have been cancelled. Claims 31-60 are new and pending.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 8/4/14, 8/5/14, 8/7/14, 8/14/14, 8/15/14 and 8/25/14 were filed before a first action on the merits. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory double patenting rejection is appropriate where the claims at issue are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir.

1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit http://www.uspto.gov/forms/. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp.

Claims 31-60 are rejected on the ground of nonstatutory double patenting as being unpatentable over:

1. Claims 1-44 of U.S. Patent No. 8795741;
2. Claims 1-25 of U.S. Patent No. 8431163;
3. Claims 1-29 of U.S. Patent No. 8282966;
4. Claims 1-30 of U.S. Patent No. 8293284; and

5. Claims 31-60 of earlier filed U.S. Application 14451057.

Although the claims at issue are not identical, they are not patentably distinct from each other because all the patents and patent application are directed to methods of administering 20 ppm inhaled nitric oxide to children/neonates to reduce the risk of pulmonary edema, and thus improve the safety of treating hypoxic respiratory failure in neoates/pediatric patients, and excluding children from treatment that have left ventricular dysfunction. Treatment for 14 days, administration until hypoxia has resolved and further therapeutic treatment of select patients by mechanical ventilation, vasodilators, i.v. fluids and bicarbonate therapy is merely judicious selection of known therapies by the ordinary artisan. Discontinuation of therapy is also a decision performed by the ordinary artisan and an obvious choice.

Consequently, the ordinary artisan would have recognized the obvious variation of the instant subject matter over the patented subject matter.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Kwon can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ERNST V ARNOLD/
Primary Examiner, Art Unit 1613

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 3860

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
14/454,373	08/07/2014 RULE	424	1613	26047-0003011

APPLICANTS

INO Therapeutics LLC, Hampton, NJ, Assignee (with 37 CFR 1.172 Interest);

INVENTORS

James S. Baldassarre, Doylestown, PA;

**** CONTINUING DATA ***************************

This application is a CON of 14/451,057 08/04/2014
which is a CON of 13/683,417 11/21/2012 PAT 8795741
which is a CON of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,417 11/21/2012
is a CON of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN
and said 14/451,057 08/04/2014
is a DIV of 13/683,444 11/21/2012
which is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,444 11/21/2012
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
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This application 14/454,373 08/07/2014
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is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN

**** FOREIGN APPLICATIONS ***************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
08/15/2014

Foreign Priority claimed ☐ Yes ☑ No 35 USC 119(a-d) conditions met ☐ Yes ☑ No Verified and Acknowledged /ERNST V ARNOLD/ Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		PA	0	30	4

ADDRESS

Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440
UNITED STATES

Inventor Information for 14/454373

Inventor Name	City	State/Country
BALDASSARRE, JAMES S.	DOYLESTOWN	PENNSYLVANIA

AppIn Info | Contents | Petition Info | Atty/Agent Info | Continuity Data | Foreign Data | **Inventors** | Applicants | Address | Fees | Post Info | Pre Gr

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Receipt date: 08/15/2014
Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/494,598, mailed August 13, 2010 (26 pages)	☐
	2	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/494,598, mailed September 10, 2010 (2 pages)	☐
	3	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, mailed September 23, 2010 (26 pages)	☐
	4	Lee & Hayes, Reply in U.S. Serial No. 12/820,866, filed October 1, 2010 (22 pages)	☐
	5	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, mailed November 2, 2010 (25 pages)	☐
	6	Lee & Hayes, Reply in U.S. Serial No. 12/820,866, filed January 14, 2011 (12 pages)	☐
	7	U.S. Examiner Ernst V. Arnold, Advisory Action in U.S. Serial No. 12/820,866, mailed February 23, 2011 (2 pages)	☐
	8	Lee & Hayes, Reply After Final in U.S. Serial No. 12/820,866, filed March 1, 2011 (9 pages)	☐
	9	Lee & Hayes, Reply After Final in U.S. Serial No. 12/820,866, filed March 3, 2011 (5 pages)	☐
	10	U.S. Examiner Ernst V. Arnold, Advisory Action in U.S. Serial No. 12/820,866, mailed March 25, 2011 (3 pages)	☐
	11	Lee & Hayes, Reply After Final in U.S. Serial No. 12/820,866, filed May 2, 2011 (9 pages)	☐

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	12	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, mailed June 8, 2011 (32 pages)	☐
	13	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,866, August 24, 2011 (23 pages)	☐
	14	Fish & Richardson, P.C., Reply Brief in U.S. Serial No. 12/820,866, filed December 16, 2011 (21 pages)	☐
	15	Fish & Richardson, P.C., Supplement to Reply Brief in U.S. Serial No. 12/820,866, filed January 3, 2012 (3 pages)	☐
	16	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed August 17, 2010 (33 pages)	☐
	17	Lee & Hayes, Reply Amendment in U.S. Serial No. 12/820,980, filed September 17, 2010 (25 pages)	☐
	18	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed October 28, 2010 (23 pages)	☐
	19	U.S. Examiner Ernst V. Arnold, Supplemental Office Action in U.S. Serial No. 12/820,980, mailed November 2, 2010 (4 pages)	☐
	20	Lee & Hayes, Reply after Final in U.S. Serial No. 12/820,980, filed November 12, 2010 (53 pages)	☐
	21	U.S. Examiner Ernst V. Arnold, Advisory Action in U.S. Serial No. 12/820,980, mailed November 29, 2010 (3 pages)	☐
	22	Lee & Hayes, Reply after Final in U.S. Serial No. 12/820,980, filed May 2, 2011 (23 pages)	☐

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	23	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed June 10, 2011 (29 pages)	☐
	24	Lee & Hayes, Amendment in Reply to Office Action in U.S. Serial No. 12/820,980, filed July 11, 2011 (115 pages)	☐
	25	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed September 9, 2011 (25 pages)	☐
	26	U.S. Examiner Ernst V. Arnold, Notice of Abandonment in U.S. Serial No. 12/820,980, mailed April 11, 2012 (2 pages)	☐
	27	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed August 13, 2010 (24 pages)	☐
	28	Lee & Hayes, Response to Office Action in U.S. Serial No. 12/821,020, filed February 14, 2011 (18 pages)	☐
	29	Lee & Hayes, Supplemental Reply Amendment in U.S. Serial No. 12/821,020, filed April 12, 2011 (9 pages)	☐
	30	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed June 27, 2011 (28 pages)	☐
	31	Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Serial No. 12/821,020, filed December 27, 2011 (31 pages)	☐
	32	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed January 31, 2012 (23 pages)	☐
	33	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed April 17, 2012 (4 pages)	☐

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	34	Fish & Richardson, P.C., Statement of Substance of Interview and Comments on Examiner's Interview Summary, in U.S. Serial No. 12/821,020, filed April 23, 2012 (8 pages)	☐
	35	Fish & Richardson, P.C., Supplemental Amendment in U.S. Serial No. 12/821,020, filed April 30, 2012 (10 pages)	☐
	36	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed June 15, 2012 (56 pages)	☐
	37	Fish & Richardson, P.C., Amendment in U.S. Serial No. 12/821,020, filed August 15, 2012 (15 pages)	☐
	38	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed August 17, 2010 (32 pages)	☐
	39	Lee & Hayes, Reply in U.S. Serial No. 12/821,041, filed February 14, 2011 (28 pages)	☐
	40	Lee & Hayes, Supplemental Reply in U.S. Serial No. 12/821,041, filed April 13, 2011 (9 pages)	☐
	41	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed June 27, 2011 (35 pages)	☐
	42	Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Serial No. 12/821,041, filed January 6, 2012 (155 pages)	☐
	43	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed February 10, 2012 (36 pages)	☐
	44	Fish & Richardson, P.C., Supplemental Amendment and Remarks in U.S. Serial No. 12/821,041, filed May 11, 2012 (32 pages)	☐

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	Attorney Docket Number	26047-0003011

	45	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed June 19, 2012 (61 pages)	☐
	46	Fish & Richardson, P.C., Amendment in Reply to Office Action in U.S. Serial No. 12/821,041, filed August 15, 2012 (17 pages)	☐
	47	Lee & Hayes, Amendment in Reply to Office Action in U.S. Serial No. 12/820,866, filed July 8, 2011 (23 pages)	☐
	48	Fish & Richardson, Brief on Appeal in U.S. Serial No. 12/820,866, filed October 4, 2011 (211 pages)	☐
	49	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed January 25, 2012 (4 pages)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature	/Ernst Arnold/	Date Considered	09/08/2014

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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Receipt date: 08/15/2014	Application Number	14454373
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
(Not for submission under 37 CFR 1.99)	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-15
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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Receipt date: 08/15/2014

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

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	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

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☒ A certification statement is not submitted herewith.

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A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature		Date (YYYY-MM-DD)	2014-08-04
Name/Print	Janis K. Fraser	Registration Number	34819

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-14
Name/Print	Janis K. Fraser	Registration Number	34819

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	38	Kinsella et al., "Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial," The Lancet, Vol. 354, pages 1061-1065 (1999)	☐
	39	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
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	44	Field, "Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Randomised Controlled Trial (ISRCTN 17821339)," Pediatrics Journal, Vol. 115, pages 926-936 (2005) DOI: 10.1542/peds.2004-1209	☐

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Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	14454373	BALDASSARRE, JAMES S.
	Examiner	Art Unit
	ERNST V ARNOLD	1613

CPC- SEARCHED		
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	2	5651358	A	1997-07-29	Briend	
	3	5873359	A	1999-02-23	Zapol	
	4	6063407	A	2000-05-16	Zapol	
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	1	20020185126	A1	2002-12-12	Krebs	
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	4	20090018136	A1	2009-01-15	Oppenheimer	
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	1	EP1682672	EP		2006-07-26			☐

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	2	WO2005004884	WO		2005-01-20			☐
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	1	Adatia et al., "Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hypertension Before Transplantation," Journal of the American College of Cardiology, Elsevier, New York, NY, Vol. 25, No. 7, page 1663, June 1, 1995	☐
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	3	Al-Alaiyan et al., "Inhaled nitric oxide in persistent pulmonary hypertension of the newborn refractory to high-frequency ventilation," Crit. Care, Vol. 3, No. 1, pages 7-10 (1999)	☐
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S5	10	((baldassarre.in. or "INO.as") and ((inhaled adj nitric) and (ventricular with dysfunction) and edema).clm.)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT	OR	ON	2014/09/05 08:42
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Receipt date: 08/08/2014	Application Number	14454373 14454373 - GAU: 1613
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	First Named Inventor	Baldassarre
(Not for submission under 37 CFR 1.99)	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

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Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-08
Name/Print	Janis K. Fraser	Registration Number	34819

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Decision Granting Request for Prioritized Examination (Track I or After RCE)	Application No.: 14/454,373

1. THE REQUEST FILED 8/7//14 IS **GRANTED.**

The above-identified application has met the requirements for prioritized examination

A. ☒ for an original nonprovisional application (Track I).
B. ☐ for an application undergoing continued examination (RCE).

2. **The above-identified application will undergo prioritized examination.** The application will be accorded special status throughout its entire course of prosecution until one of the following occurs:

A. filing a **petition for extension of time** to extend the time period for filing a reply;
B. filing an **amendment to amend the application to contain more than four independent claims, more than thirty total claims**, or a multiple dependent claim;
C. filing a **request for continued examination**;
D. filing a notice of appeal;
E. filing a request for suspension of action;
F. mailing of a notice of allowance;
G. mailing of a final Office action;
H. completion of examination as defined in 37 CFR 41.102; or
I. abandonment of the application.

Telephone inquiries with regard to this decision should be directed to Terri Johnson at 571-272-2991

/Terri Johnson/ — Paralegal Specialist

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	1	Fish & Richardson P.C., Supplemental Remarks in U.S. Serial No. 12/821,020, filed May 9, 2012 (22 pages)	☐
	2	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed January 25, 2012 (4 pages)	☐
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	8	Communication from Canadian Intellectual Property Office dated March 19, 2013, enclosing Protest from Robic regarding Canadian patent application no. 2,671,029 (42 pages)	☐
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	34	Rosales et al., "Adverse Hemodynamic Effects Observed with Inhaled Nitric Oxide After Surgical Repair of Total Anomalous Pulmonary Venous Return," Pediatric Cardiology, 20:224-226 (1999)	☐
	35	PRAXAIR, INC. Protest filed against CA2,671,029 on June 2, 2014 (38 pages)	☐
	36	Prior art notice issued in CA267102 on August 9, 2013 (51 pages)	☐
	37	Stewart et al.; Hypoxic Respiratory Failure: Diagnosis and Treatment, 36th Annual Pacific Northwest Regional Respiratory Care Conference and Scientific Assembly; Apr. 26, 2009; pp. 1-71	☐
	38	Kinsella et al., "Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomised controlled trial," The Lancet, Vol. 354, pages 1061-1065 (1999)	☐
	39	Loh et al., "Cardiovascular Effects of Inhaled Nitric Oxide in Patients with Left Ventricular Dysfunction," Circulation, Vol. 90, pages 2780-2785 (1994)	☐
	40	Martinez et al., "Dermatological Cryosurgery in Primary Care with Dimethyl Ether Propane Spray in Comparison with Liquid Nitrogen," Atencion Primaria, Vol. 18, No. 5, pages 211 and 216 (1996)	☐
	41	Adatia et al., "Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hypertension Before Transplantation," Journal of the American College of Cardiology, Elsevier, New York, NY, Vol. 25, No. 7, page 1663, June 1, 1995	☐
	42	Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," Pediatric Cardiol., Vol. 23, pages 20-26 (2002)	☐
	43	Bland, "Pulmonary vascular dysfunction in preterm lambs with chronic lung disease," Am J Physical Lung Cell Mol. Physiol., Vol. 285: L76-L85 (2003)	☐
	44	Field, "Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure: The INNOVO Multicentre Randomised Controlled Trial (ISRCTN 17821339)," Pediatrics Journal, Vol. 115, pages 926-936 (2005) DOI: 10.1542/peds.2004-1209	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	45	Green, "Patent Ductus Arteriosus Demonstrating Shunting of Blood," Figure from presentation given 1/10/2011	☐
	46	INO Therapeutics, NCT00551642 at ClinicalTrials.gov (2007)	☐
	47		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-25
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	19959297
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	25-AUG-2014
Filing Date:	07-AUG-2014
Time Stamp:	17:49:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS.pdf	63196 83ec4bfc9ad5c29896dcc3f123e328a5bd0da96a	no	1

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	615487 f8d2fe6e1c1b631fc61ce5f786fb2ccaa41be7a9	no	8
Warnings:					
Information:					
A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.					
3	Non Patent Literature	Prior.pdf	2663485 43ce84564d9d064e826444ac45e8c812cb17db9c	no	38
Warnings:					
Information:					
4	Non Patent Literature	Rosales.pdf	3360703 e17690f3f5539e78723d6ec621c22a54e25b2b6f	no	51
Warnings:					
Information:					
5	Non Patent Literature	Stew.pdf	2770914 0a7f1b9dbad81f15cbc16ad6e749987c6cfd389a	no	71
Warnings:					
Information:					
			Total Files Size (in bytes):	9473785	

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<u>New Applications Under 35 U.S.C. 111</u>
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

<u>National Stage of an International Application under 35 U.S.C. 371</u>
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

<u>New International Application Filed with the USPTO as a Receiving Office</u>
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SIXTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. References 1-34 and 38-46 were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application. Copies of references 35-37 are attached. References 38-46 were cited in PTO-SB-08 Forms previously submitted in the present application and are being re-cited here to correct typographical errors present in the prior submissions.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 25, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

23280565.doc

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 14/454,373

APPLICATION AS FILED - PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY FEE($)
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	70		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	300		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	360		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10	x 40 =	400	OR		
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1	x 210 =	210			
APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				0.00			
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	1340		TOTAL	

APPLICATION AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE($)	SMALL ENTITY ADDITIONAL FEE($)	OR	OTHER THAN SMALL ENTITY RATE($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE($)	ADDITIONAL FEE($)	OR	RATE($)	ADDITIONAL FEE($)
Total (37 CFR 1.16(i))	*	Minus	**	=	x =		OR	x =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	x =		OR	x =	
Application Size Fee (37 CFR 1.16(s))									
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
14/454,373	08/07/2014	1616	1340	26047-0003011	30	4

CONFIRMATION NO. 3860

94169
Fish & Richardson PC
P.O.Box 1022
minneapolis, MN 55440

FILING RECEIPT

OC000000070224328

Date Mailed: 08/18/2014

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

James S. Baldassarre, Doylestown, PA;

Applicant(s)

INO Therapeutics LLC, Hampton, NJ

Assignment For Published Patent Application

INO THERAPEUTICS LLC, Hampton, NJ

Power of Attorney: The patent practitioners associated with Customer Number 94169

Domestic Priority data as claimed by applicant

This application is a CON of 14/451,057 08/04/2014
which is a CON of 13/683,417 11/21/2012 PAT 8795741
which is a CON of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,417 11/21/2012
is a CON of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN
and said 14/451,057 08/04/2014
is a DIV of 13/683,444 11/21/2012
which is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,444 11/21/2012
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN
This application 14/454,373

is a DIV of 13/683,444 11/21/2012
which is a DIV of 12/820,866 06/22/2010 ABN
which is a CON of 12/494,598 06/30/2009 ABN
and said 13/683,444 11/21/2012
is a DIV of 13/651,660 10/15/2012 PAT 8431163
which is a CON of 12/821,041 06/22/2010 PAT 8293284
which is a CON of 12/494,598 06/30/2009 ABN

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 08/15/2014

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 14/454,373**

Projected Publication Date: 11/27/2014

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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Doc code: IDS
Doc description: Information Disclosure Statement (IDS) Filed

PTO/SB/08a (01-10)
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/494,598, mailed August 13, 2010 (26 pages)	☐
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	14	Fish & Richardson, P.C., Reply Brief in U.S. Serial No. 12/820,866, filed December 16, 2011 (21 pages)	☐
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	17	Lee & Hayes, Reply Amendment in U.S. Serial No. 12/820,980, filed September 17, 2010 (25 pages)	☐
	18	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed October 28, 2010 (23 pages)	☐
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	20	Lee & Hayes, Reply after Final in U.S. Serial No. 12/820,980, filed November 12, 2010 (53 pages)	☐
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	23	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/820,980, mailed June 10, 2011 (29 pages)	☐
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	33	U.S. Examiner Ernst V. Arnold, Interview Summary in U.S. Serial No. 12/821,020, mailed April 17, 2012 (4 pages)	☐

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	34	Fish & Richardson, P.C., Statement of Substance of Interview and Comments on Examiner's Interview Summary, in U.S. Serial No. 12/821,020, filed April 23, 2012 (8 pages)	☐
	35	Fish & Richardson, P.C., Supplemental Amendment in U.S. Serial No. 12/821,020, filed April 30, 2012 (10 pages)	☐
	36	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,020, mailed June 15, 2012 (56 pages)	☐
	37	Fish & Richardson, P.C., Amendment in U.S. Serial No. 12/821,020, filed August 15, 2012 (15 pages)	☐
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	45	U.S. Examiner Ernst V. Arnold, Office Action in U.S. Serial No. 12/821,041, mailed June 19, 2012 (61 pages)	☐
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	48	Fish & Richardson, Brief on Appeal in U.S. Serial No. 12/820,866, filed October 4, 2011 (211 pages)	☐
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	Art Unit	
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	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

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☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-15
Name/Print	Janis K. Fraser	Registration Number	34819

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EFS ID:	19882025
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods for improving the safety of treating pediatric patients who are candidates for inhaled nitric oxide treatment
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	15-AUG-2014
Filing Date:	07-AUG-2014
Time Stamp:	17:24:24
Application Type:	Utility under 35 USC 111(a)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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FIFTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 15, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
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Customer Number 94169
Fish & Richardson P.C.
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	Attorney Docket Number	26047-0003011

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	Examiner Name	
	Attorney Docket Number	26047-0003011

	1	Ratnasamy et al., "Associations between neurohormonal and inflammatory activation and heart failure in children," American Heart Journal, pages 527-533 (2008)	☐
	2	Response filed 08/18/2010 to EP Search Report dated 05/10/10 for EP09251949	☐
	3	Ricciardi et al., "Inhaled Nitric Oxide in Primary Pulmonary Hypertension: A Safe and Effective Agent for Predicting Response to Nifedipine," Journal of the American College of Cardiology (JACC,) Vol. 32, No. 4, pages 1068-1073 (1998)	☐
	4	Roberts, "Inhaled Nitric Oxide and Persistent Pulmonary Hypertension of the Newborn," The New England Journal of Medicine, Vol. 336, No 9, pages 605-610 (1997)	☐
	5	Roberts, "Nitric Oxide and the Lung," Marcel Dekker, Inc., New York, NY, pages 333-363 (1997)	☐
	6	Rosales et al., "Hemodynamic Effects Observed with Inhaled Nitric Oxide After Surgical Repair of Total Anamolous Pulmonary Venous Return," Pediatric Cardiology, Vol. 20, pages 224-226 (1999)	☐
	7	Rosenberg, "Inhaled nitric oxide in the premature infant with severe hypoxemic respiratory failure: A time for caution," The Journal of Pediatrics, Volume 133, Issue 6 , pages 720-722 (1998)	☐
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	12	Shapiro et al., "Diagnostic Dilemmas: Diastolic Heart Failure Causing Pulmonary Hypertension and Pulmonary Hypertension Causing Diastolic Dysfunction," Advances in Pulmonary Hypertension, Vol. 5(1), pages 13-20 (2006) http://www.phaonlineuniv.org/sites/default/files/spr_2006.pdf	☐
	13	"Sibutramine-metformin Combination vs. Sibutramine and Metformin Monotherapy in Obese Patients, page 3, ClinicalTrials.gov, <<http://clinicaltrials.gov/ct2/showNCT00941382>> Sponsored by Laboratorios Silanes S.A. de C.V. and Jorge González Canudas, July 15, 2009	☐
	14	Singh et al., "Nitric Oxide, the biological mediator of the decade: fact or fiction?," Eur. Respir. J. , Vol. 10, pages 699-707 (1997)	☐
	15	Smyth, "Inhaled nitric oxide treatment for preterm infants with hypoxic respiratory failure," Thorax, Vol. 55 (Suppl 1), pages S51-S55 (2000)	☐
	16	Somarriba et al., "Exercise rehabilitation in pediatric cardiomyopathy," Progress in Pediatric Cardiology, Vol. 25, pages 91-102 (2008)	☐
	17	Soto et al., "Cardiopulmonary Hemodynamics in Pulmonary Hypertension: Pressure Tracings, Waveforms, and More," Advances in Pulmonary Hypertension Winter, Vol. 7(4), pages 386-393 (2008)	☐
	18	Steinhorn et al., "Inhaled nitric oxide enhances oxygenation but not survival in infants with alveolar capillary dysplasia," The Journal of Pediatrics, Vol. 130(3), pages 417-422 (1997)	☐
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	23	Toshniwal, et al., "Study of Comparative Effects of Oral Clonidine vs. Oral Diazepam Pre-Medication on the Extent and Duration of Sensory Blockade in Patients Undergoing Vaginal Hysterectomy Under Spinal Anaesthesia", Internet Journal of Anesthesiology (2009) <<http://www.britannica.com/bps/additionalcontent/18/41575551/Study-of-Comparative-Effects-Oral-Clonidine-vs-Oral-Diazepam-Pre-Medication-on-the-Extent-and-Duration-of-Sensory-Blockade-in-Patients-Undergoing-Vaginal-Hysterectomy-Under-Spinal-Anaesthesia>>	☐
	24	The American Illustrated Medical Dictionary (Dorland, 7th ed., page 113) (1914)	☐
	25	The Effects of Nitric Oxide for Inhalation on the Development of Chronic Lung Disease in Pre-Term Infants, from ClinicalTrials.gov archive, NCT00551642, 10/30/2007, 3 pages	☐
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	29	Towbin et al., "Incidence, Causes, and Outcomes of Dilated Cardiomyopathy in Children," JAMA, Vol. 296, No. 15, pages 1867-1876 (2006)	☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	43	Wilkinson et al., "Epidemiological and outcomes research in children with pediatric cardiomyopathy; discussions from the international workshop on primary and idiopathic cardiomyopathies in children," Progress in Pediatric Cardiology, Vol. 25, pages 23-25 (2008)	☐
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-14
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	19871185
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	14-AUG-2014
Filing Date:	
Time Stamp:	17:16:15
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS.pdf	63010 3d22ecae787d8a1a25740a877a3eebdfc13abeb8	no	1

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2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	616030 8407dcb6158fcf48aaafb7f464c7288401257e3b	no	8

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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

FOURTH INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 14, 2014

/Janis K. Fraser/
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title *(as amended)*	:	METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Track 1 status has been requested for this application. Prior to examination, please amend the application as indicated on the following pages.

Amendments to the Specification:

Replace the title on page 1 with the following new title:

METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

Amendments to the Abstract:

Delete the previous abstract at page 29 and add the following new abstract:

Disclosed are methods of reducing the risk that a medical treatment comprising inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure in pediatric patients, leading to pulmonary edema. The methods include avoiding or discontinuing administration of inhaled nitric oxide to a pediatric patient determined to have pre-existing left ventricular dysfunction but who otherwise is a candidate for inhaled nitric oxide treatment (e.g., for pulmonary hypertension), and administering inhaled nitric oxide to pediatric patients who are candidates for such treatment and who are determined not to have pre-existing left ventricular dysfunction.

Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1-30. (Canceled)

31. (New) A method of improving the safety of treating hypoxic respiratory failure in neonates by reducing the risk of inducing pulmonary edema, the method comprising:

(a) identifying a plurality of neonatal patients who have hypoxic respiratory failure;

(b) determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

(c) administering a first treatment regimen to the first patient, wherein the first treatment regimen comprises administration of 20 ppm inhaled nitric oxide for 14 days or until the first patient's hypoxia has resolved;

(d) determining that a second patient of the plurality has pre-existing left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(e) based on the determination of (d), selecting and administering a second treatment regimen to the second patient, wherein the second treatment regimen does not comprise either (i) administration of inhaled nitric oxide for 14 days or (ii) administration of inhaled nitric oxide until the second patient's hypoxia has resolved, and does comprise one or more other therapies selected from vasodilators, intravenous fluids, bicarbonate therapy and mechanical ventilation.

32. (New) The method of claim 31, wherein the second treatment regimen comprises mechanical ventilation.

33. (New) The method of claim 31, wherein the second treatment regimen does not comprise administration of inhaled nitric oxide.

34. (New) The method of claim 31, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide, but discontinuing the administration upon determining that inhaling nitric oxide has increased the second patient's pulmonary capillary wedge pressure (PCWP), the discontinuation being at a point before the second patient has received 14 days of inhaled nitric oxide administration and before the second patient's hypoxia has resolved.

35. (New) The method of claim 31, wherein the second treatment regimen comprises beginning administration of inhaled nitric oxide, but discontinuing the administration upon determining that inhaling nitric oxide has induced pulmonary edema in the second patient, the discontinuation being at a point before the second patient has received 14 days of inhaled nitric oxide administration and before the second patient's hypoxia has resolved.

36. (New) The method of claim 31, comprising performing a diagnostic process to identify the second patient as having hypoxic respiratory failure.

37. (New) The method of claim 36, wherein the diagnostic process comprises echocardiography.

38. (New) The method of claim 31, wherein the first and second patients are term or near-term neonates.

39. (New) The method of claim 31, wherein the selection of the second treatment regimen is based not only on a determination that the second patient is at particular risk of pulmonary edema, but also on a determination that the second patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

40. (New) A method of improving the safety of treating hypoxic respiratory failure in neonates by reducing the risk of inducing pulmonary edema, the method comprising:

(a) identifying a plurality of neonatal patients who have hypoxic respiratory failure;

(b) determining that a first patient of the plurality does not have pre-existing left ventricular dysfunction;

(c) administering a first treatment regimen to the first patient, wherein the first treatment regimen comprises administration of 20 ppm inhaled nitric oxide;

(d) determining that a second patient of the plurality has pre-existing left ventricular dysfunction, so is at particular risk of pulmonary edema upon treatment with inhaled nitric oxide; and

(e) based on the determination of (d), selecting and administering a second treatment regimen to the second patient, wherein the second treatment regimen does not comprise administration of inhaled nitric oxide, and does comprise one or more other therapies selected from vasodilators, intravenous fluids, bicarbonate therapy and mechanical ventilation.

41. (New) The method of claim 40, wherein the second treatment regimen comprises mechanical ventilation.

42. (New) The method of claim 40, comprising performing a diagnostic process to identify the second patient as having hypoxic respiratory failure.

43. (New) The method of claim 42, wherein the diagnostic process comprises echocardiography.

44. (New) The method of claim 40, wherein the second patient is a term or near-term neonate.

45. (New) The method of claim 40, wherein the selection of the second treatment regimen is based not only on a determination that the second patient is at particular risk of

pulmonary edema, but also on a determination that the second patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

46. (New) A method of improving the safety of treating pulmonary hypertension in pediatric patients by reducing the risk of inducing pulmonary edema, the method comprising:

(a) identifying a pediatric patient having pulmonary hypertension and pre-existing left ventricular dysfunction;

(b) determining that, because the patient has pre-existing left ventricular dysfunction, the patient is at particular risk of increased PCWP leading to pulmonary edema, when treated with inhaled nitric oxide;

(c) treating the patient with 20 ppm inhaled nitric oxide;

(d) determining that the patient's PCWP increased during the treatment; and

(e) based on the determinations of (b) and (d), discontinuing the inhaled nitric oxide treatment.

47. (New) The method of claim 46, wherein the pulmonary hypertension is associated with hypoxia, and the discontinuation occurs at a point before the patient has received 14 days of inhaled nitric oxide administration and before the patient's hypoxia has resolved.

48. (New) The method of claim 46, wherein the discontinuation is based not only on a determination that the patient is at particular risk of increased PCWP leading to pulmonary edema, but also on a determination that the patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

49. (New) The method of claim 46, comprising performing a diagnostic process to identify the patient as having pulmonary hypertension.

50. (New) The method of claim 46, wherein the patient is a neonate.

51. (New) The method of claim 46, wherein the patient is a term or near-term neonate.

52. (New) The method of claim 46, wherein the patient's pulmonary hypertension is associated with hypoxic respiratory failure.

53. (New) The method of claim 52, wherein the patient is a neonate.

54. (New) A method of improving the safety of treating hypoxic respiratory failure in neonates by reducing the risk of inducing pulmonary edema, the method comprising:

(a) identifying a neonatal patient as having hypoxic respiratory failure and pre-existing left ventricular dysfunction;

(b) determining that, because the patient has pre-existing left ventricular dysfunction, the patient is at particular risk of pulmonary edema when treated with inhaled nitric oxide;

(c) treating the patient with 20 ppm inhaled nitric oxide; and

(d) discontinuing the inhaled nitric oxide treatment due to the determination of (b).

55. (New) The method of claim 54, wherein the discontinuation occurs at a point before the patient has received 14 days of inhaled nitric oxide administration and before the patient's hypoxia has resolved.

56. (New) The method of claim 54, comprising performing a diagnostic process to identify the patient as having hypoxic respiratory failure.

57. (New) The method of claim 56, wherein the diagnostic process comprises echocardiography.

58. (New) The method of claim 54, wherein the patient is a term or near-term neonate.

59. (New) The method of claim 55, wherein the patient is a term or near-term neonate.

60. (New) The method of claim 54, wherein the discontinuation is due not only to the determination that the patient is at particular risk of pulmonary edema, but also due to a determination that the patient is at particular risk of other serious adverse events, upon treatment with inhaled nitric oxide.

REMARKS

The above amendment cancels all of the original claims 1-30 and replaces them with new claims 31-60. Support for the new claims can be found throughout the original specification and claims (including the specification and claims of the original grandparent application (USSN 12/494,598) filed June 30, 2009)): for example, at paragraphs [0005], [0008], [0009], [0014], [0016], [0018], [0019], [0021] (which incorporates by reference the prescribing information for INOmax®), [0034], [0051], [0052], [0062] (including the table that is now numbered Table 7), and [0065], and in original claims 1, 4, 6, 8, 9, and 24. The amendment also amends the title and abstract. No new matter has been added by this amendment.

STATEMENT OF SUBSTITUTE SPECIFICATION UNDER 37 C.F.R. § 1.125

Pursuant to 37 C.F.R. § 1.125, Applicants submit a substitute specification encompassing changes being made to the specification filed on August 7, 2014. The specification is amended to revise the title, to add the priority information, to correct typographical errors, and to recite some of the text from the 2009 prescribing information for INOmax® nitric oxide for inhalation that had been incorporated by reference in the earliest priority application filed in 2009. This substitute specification introduces no new matter to the specification filed on August 7, 2014. Applicants request entry of the substitute specification.

Also attached is a marked-up version of the substitute specification, showing the changes that have been made.

Applicant asks that all claims be examined in view of the amendment to the claims.

The excess claims fee of $610 is being paid with this reply on the Electronic Filing System. Apply this and any other necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 13, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

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ABSTRACT

Disclosed are methods of reducing the risk that a medical treatment comprising inhalation of nitric oxide gas will induce an increase in pulmonary capillary wedge pressure in pediatric patients, leading to pulmonary edema. The methods include avoiding or discontinuing administration of inhaled nitric oxide to a pediatric patient determined to have pre-existing left ventricular dysfunction but who otherwise is a candidate for inhaled nitric oxide treatment (e.g., for pulmonary hypertension), and administering inhaled nitric oxide to pediatric patients who are candidates for such treatment and who are determined not to have pre-existing left ventricular dysfunction.

Electronic Patent Application Fee Transmittal

Application Number:	14454373
Filing Date:	
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003011

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	10	40	400
Independent Claims in Excess of 3	2201	1	210	210
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**610**

Electronic Acknowledgement Receipt	
EFS ID:	19860087
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	13-AUG-2014
Filing Date:	
Time Stamp:	18:23:09
Application Type:	Utility under 35 USC 111(a)

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Payment Type	Deposit Account
Payment was successfully received in RAM	$610
RAM confirmation Number	4596
Deposit Account	061050
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Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	Transmittal Letter	IDS.pdf	62556 2a2c3386abb4cdf58ebb0c58ac457fdec6ceda46	no	1
Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	615615 8f7715b6ea606d512b1c5d7ac25a1a6903acc309	no	8
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Document Description	Start	End
Preliminary Amendment	1	1
Specification	2	2
Abstract	3	3
Claims	4	9
Applicant Arguments/Remarks Made in an Amendment	10	11
Abstract	12	12

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No. :	3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

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P.O. Box 1450
Alexandria, VA 22313-1450

THIRD INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing dates of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in one or more of the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 13, 2014

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	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	1	Konduri et al., "A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure," Pediatrics, Vol. 113 No. 3, pages 559-564 (2004)	☐
	2	Krasuski et al., "Inhaled Nitric Oxide Selectively Dilates Pulmonary Vasculature in Adult Patients With Pulmonary Hypertension, Irrespective of Etiology," Journal of the American College of Cardiology (JACC), Vol. 36, No. 7, pages 2204-2211 (2000)	☐
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	12	Lipshultz, "Clinical research directions in pediatric cardiology," Current Opinion in Pediatrics, Vol. 21, pages 585-593 (2009)	☐
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	44	Office Action Response for JP2007157623 filed on 11/12/2009 (no English translation)	☐

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	45	Office Action Response to AU 2010202422 OA dated 07/09/2010, response filed 09/01/2010	☐
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Signature		Date (YYYY-MM-DD)	2014-08-04
Name/Print	Janis K. Fraser	Registration Number	34819

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METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT~~METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION~~

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] ~~Not applicable.~~This application is a continuation of U.S. Serial No. 14/451,057, filed August 4, 2014, which is a continuation of U.S. Serial No. 13/683,417 (now U.S. Patent No. 8,795,741), filed November 21, 2012, which is a continuation of U.S. Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 13/683,417 is also a continuation of U.S. Serial No. 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 14/451,057 is also a division of U.S. Application Serial No. 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a division of 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. The contents of the foregoing applications are incorporated by reference in the present application.

STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108(Suppl II):II-167-II-173; Lepore JJ et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler JW et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO.

Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and[[,]] (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a[[.]]) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and[[,]] (b[[.]]) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

[0008] Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a[[.]]) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

[0009] Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a[[.]]) identifying a patient in need of receiving iNO treatment; (b[[.]]) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c[[.]]) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus

benefit of utilizing iNO in a patient where the patient[[s]] has clinically significant LVD before administering iNO to the patient.

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric ~~oxides~~ oxide in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

[0012] In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

[0013] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate [[ ]]a PCWP $\geq$ 20 mm Hg.

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0015] In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or[[,]] associations thereof.

[0016] In another exemplary embodiment of the method, the patient population comprises children.

[0017] In another exemplary embodiment of the method, the patient population comprises adults.

[0018] In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing ~~and~~ an increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

[0019] In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary

arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) > 25 mm Hg at rest, PCWP ≤ 15 mm Hg, and[[,]] a pulmonary vascular resistance index (PVRI) > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; or[[,]] the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

[0020] In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The ~~current~~ FDA-approved prescribing information for INOmax® in effect in 2009 is incorporated herein by reference in its entirety. The DOSAGE section of the prescribing information for INOmax® states that the recommended dose of INOmax® is 20 ppm, and that treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The ADMINISTRATION section of the prescribing information says that the safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. The CONTRAINDICATIONS section

of the prescribing information states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417;950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired $O[[2]]_2$, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

[0024] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0025] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0026] As used herein, the terms "adverse event" [[or]]and "AE" (and variations thereof) mean any untoward occurrence in a subject[[,]] or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and

unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

[0027] As used herein, the terms "adverse drug reaction" [[or]]and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

[0028] As used herein, the terms "serious adverse event" [[or]]and "SAE" (or "serious adverse drug reaction" [[or]]and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or[[,]] is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above--these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

[0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic

dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

[0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include ~~measure~~ measuring by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). ~~Measure~~ Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

[0031] In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore ~~only~~ of direct relevance only in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The ~~terms~~ term "left ventricular afterload" (and variations thereof) ~~refer~~ refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease.

Hypertension (iIncreased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an ~~increase~~ increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload ~~thus~~, and actively inflates in diastole, increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body.

These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening

arterial oxygenation. (*See* Rubin LJ, Kerr KM, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult*, *2d Ed.*, Parillo JE, Dellinger RP (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella JP, Abman SH, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course*, *2d Ed.*, Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

[0038] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0039] CINRGI study. (See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $PaO_2 > 60$ mm Hg and a pH < 7.55 were weaned to 5 ppm

INOmax® or placebo. The primary results from the CINRGI study are presented in Table [[4]]1. ECMO was the primary endpoint of the study.

Table 1: Summary of Clinical Results from CINRGI Study

	Placebo	INOmax®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[0041] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0042] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were

initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mmHg, partial = 10–20 mm Hg, no response = < 10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

[0044] Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

[0045] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological ~~squeal~~sequelae.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

[0048] The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

Table 3: ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n=89)	Inhaled NO (n=97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

[0049] Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1: INOT22 STUDY

[0051] The INOT22 study, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to ~~access~~ assess the safety and

effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary ~~criteria~~ criterion of a PCWP less than 20 [[gmm]]mm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

[0054] The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by

center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

[0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) ($p = 0.007$) and that for O_2 was 1.3 WU·m^2 ($p = 0.004$). While the change from baseline in SVRI with NO alone was -0.2 WU·m^2 ($p = 0.899$) which demonstrates a lack of systemic effect.

Table 4: SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.
Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

[0056] The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

Table 5: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

[0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

Table 6: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

[0058] NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG)

decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was [[ ]]thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they [[ ]]would be most likely at-risk for these SAEs.

[0062] SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also ~~lead~~ led to

discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table [[5]]7 below.

Table [[5]]7: Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

[0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

[0064] Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi EA et al., 1994; Semigran MJ et al., 1994).

[0065] In the INOT22 study, 10 of the total 134 patients had a baseline PCWP $\geq$ 18 mm Hg (7.5%), of which[[,]] 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

[0066] Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

[0067] Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as ~~iNO~~ iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

[0068] It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor CJ et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

[0069] The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP > 20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case

basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

METHODS FOR IMPROVING THE SAFETY OF TREATING PEDIATRIC PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation of U.S. Serial No. 14/451,057, filed August 4, 2014, which is a continuation of U.S. Serial No. 13/683,417 (now U.S. Patent No. 8,795,741), filed November 21, 2012, which is a continuation of U.S. Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 13/683,417 is also a continuation of U.S. Serial No. 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. U.S. Serial No. 14/451,057 is also a division of U.S. Application Serial No. 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. This application is also a division of 13/683,444, filed November 21, 2012, which is a division of U.S. Application Serial No. 12/820,866, filed June 22, 2010, and now abandoned, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009. U.S. Application Serial No. 13/683,444 is also a division of 13/651,660 (now U.S. Patent No. 8,431,163), filed October 15, 2012, which is a continuation of U.S. Application Serial No. 12/821,041 (now U.S. Patent No. 8,293,284), filed June 22, 2010, which is a continuation of U.S. Application Serial No. 12/494,598, filed June 30, 2009, and now abandoned. The contents of the foregoing applications are incorporated by reference in the present application.

STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108(Suppl II):II-167-II-173; Lepore JJ et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler JW et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and (b) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

[0008] Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

[0009] Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a) identifying a patient in need of receiving iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c) administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patient has clinically significant LVD before administering iNO to the patient.

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in

human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

[0012] In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

[0013] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP $\geq$ 20 mm Hg.

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0015] In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or associations thereof.

[0016] In another exemplary embodiment of the method, the patient population comprises children.

[0017] In another exemplary embodiment of the method, the patient population comprises adults.

[0018] In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing an increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

[0019] In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) > 25 mm Hg at rest, PCWP $\leq$ 15 mm Hg, and a pulmonary vascular resistance index (PVRI) > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25

mm Hg at rest and PVRI > 3 u·m^2; or the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

[0020] In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The FDA-approved prescribing information for INOmax® in effect in 2009 is incorporated herein by reference in its entirety. The DOSAGE section of the prescribing information for INOmax® states that the recommended dose of INOmax® is 20 ppm, and that treatment should be maintained up to 14 days or until the underlying oxygen desaturation has resolved and the neonate is ready to be weaned from INOmax® therapy. The ADMINISTRATION section of the prescribing information says that the safety and effectiveness of inhaled nitric oxide have been established in a population receiving other therapies for hypoxic respiratory failure, including vasodilators, intravenous fluids, bicarbonate therapy, and mechanical ventilation. The CONTRAINDICATIONS section of the prescribing information states that INOmax® should not be used in the treatment of neonates known to be dependent on right-to-left shunting of blood.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is

administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417;950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery, and a backup NO delivery capability.

[0024] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0025] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0026] As used herein, the terms "adverse event" and "AE" (and variations thereof) mean any untoward occurrence in a subject or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

[0027] As used herein, the terms "adverse drug reaction" and "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

[0028] As used herein, the terms "serious adverse event" and "SAE" (or "serious adverse drug reaction" and "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above--these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

[0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

[0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measuring by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measurement of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

[0031] In cardiac physiology, the term "afterload" is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore of direct relevance only in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The term "left ventricular afterload" (and variations thereof) refers to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure, since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood

pressure would fall, due to regurgitation. This would result in an increased pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole, increasing forward blood flow by reducing afterload ~~thus~~, and actively inflates in diastole, increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and it has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn (PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult

patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (*See* Rubin LJ, Kerr KM, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult*, *2d Ed.*, Parillo JE, Dellinger RP (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella JP, Abman SH, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course*, *2d Ed.*, Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude

and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

[0038] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0039] CINRGI study. (See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $PaO_2 > 60$ mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 1. ECMO was the primary endpoint of the study.

Table 1: Summary of Clinical Results from CINRGI Study

	Placebo	**INOmax®**	**P value**
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001

	Placebo	INOmax®	P value
Death	5/89 (6%)	3/97 (3%)	0.48

[0041] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0042] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mmHg, partial = 10–20 mm Hg, no response = < 10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

[0044] Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

[0045] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological sequelae.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

[0048] The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

Table 3: ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n=89)	Inhaled NO (n=97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

[0049] Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1: INOT22 STUDY

[0051] The INOT22 study, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to assess the safety and

effectiveness of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criterion of a PCWP less than 20 mm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

[0054] The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by

center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

[0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) ($p = 0.007$) and that for O_2 was 1.3 WU·m^2 ($p = 0.004$). While the change from baseline in SVRI with NO alone was -0.2 WU·m^2 ($p = 0.899$) which demonstrates a lack of systemic effect.

Table 4: SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.
Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

[0056] The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

Table 5: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

[0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

Table 6: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

[0058] NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG)

decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

[0062] SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also led to

discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 7 below.

Table 7: Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

[0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

[0064] Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi EA et al., 1994; Semigran MJ et al., 1994).

[0065] In the INOT22 study, 10 of the total 134 patients had a baseline PCWP $\geq$ 18 mm Hg (7.5%), of which 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%), compared to 6.5% for the entire cohort.

[0066] Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

[0067] Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO's being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

[0068] It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor CJ et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

[0069] The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP > 20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case

basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/454,373	Filing Date 08/07/2014	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	08/13/2014	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 30	Minus	** 30	= 0	X $40 =	0
	Independent (37 CFR 1.16(h))	* 4	Minus	***4	= 0	X $210 =	0
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**0**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
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The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

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/EVA GILLIS/

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	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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	1	Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), NCT00005773 at ClinicalTrials.gov (2008)	☐
	2	European Patent Office minutes of oral proceedings in EP 09 251 949.5, with allowable claims (7 pages), dated May 23, 2012	☐
	3	Fauci et al., Harrison's Principles of Internal Medicine, pages1287-1291 and 1360, 12th edition, McGraw Hill (1998)	☐
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	5	Ferguson et al., "Inhaled nitric oxide for hypoxemic respiratory failure: Passing bad gas?," Canadian Medical Association Journal, Vol. 162 (1), pages 85-86 (2000)	☐
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	Examiner Name	
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	23	Huddleston, "Indications for heart transplantation in children," Progress in Pediatric Cardiology, Vol. 26, pages 3-9 (2009)	☐
	24	Husten, "Dronedarone is Less Effective, But Safer Than Amiodarone in Atrial Fibrillation," page 3, (2009) http://www.npci.org.uk/blog/?p=778	☐
	25	Hurford et al., "Nitric Oxide," Biology and Pathobiology, Academic Press, Chapter 56, pages 931-945 (2000)	☐
	26	Ichinose et al., "Inhaled Nitric Oxide - A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential," Circulation, Vol. 109, pages 3106-3111 (2004)	☐
	27	Inglessis et al., "Does inhaled nitric oxide support the hemodynamic of spontaneous breathing patients with cardiogenic shock related to right ventricular myocardial infarction? Reply," JACC, Vol. 45, No. 6, pages 965-966 (2005)	☐
	28	Inglessis et al., "Hemodynamic effects of inhaled nitric oxide in right ventricular myocardial infarction and cardiogenic shock," JACC, Vol. 44, No. 4, pages 793-798 (2004)	☐
	29	Baldassarre, "Inhaled Nitric Oxide (INO) in Hypoxic Respiratory Failure, Study description, study sponsored by INO Therapeutics," ClinicalTrials.gov Identifier NCT00922532, 4 pages (2009)	☐
	30	"Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia," The Neonatal Inhaled Nitric Oxide Study Group (NINOS), Pediatrics, Vol. 99, No. 6, pages 838-845 (1997)	☐
	31	Inhaled Nitric Oxide by Oxygen Hood in Neonates, from ClinicalTrials.gov, NCT00732537, 08/08/2008	☐
	32	Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure," The Neonatal Inhaled Nitric Oxide Study Group, N. Engl. J. Med., Vol. 336, No. 9, pages 597-605 (1997)	☐
	33	Inhaled Nitric Oxide in Neonates with Elevated A-a DO2 Gradients Not Requiring Mechanical Ventilation, from ClinicalTrials.gov archive, NCT00041548, 06/23/2005, 2 pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	34	INO Therapeutics, "Comparison of Inhaled Nitric Oxide and Oxygen in Patient Reactivity during Acute Pulmonary Vasodilator Testing," downloaded from clinicaltrials.gov on April 23, 2012; first received on February 20, 2008; last updated on October 18, 2010	☐
	35	INO Therapeutics, LLC, "INOflo for Inhalation 800ppm," package leaflet, 2010	☐
	36	INO Therapeutics, NCT00041548 at ClinicalTrials.gov (2005)	☐
	37	INO Thereapeutics, NCT00551642 at ClinicalTrials.gov (2007)	☐
	38	INOmax (nitric oxide) for inhalation 100 and 800 ppm (parts per million), drug label insert, 2007, 2 pages	☐
	39	Ivy et al., "Dipyridamole attenuates rebound pulmonary hypertension after inhaled nitric oxide withdrawal in postoperative congenital heart disease," J. Thorac. Cardiovasc. Surg.; Vol. 115, pages 875-882 (1998)	☐
	40	James et al., "Treatment of heart failure in children," Current Pediatrics, Vol. 15, 539-548 (2005)	☐
	41	JP 2009157623 Office Action dated 02/15/2011, 3 pages	☐
	42	JP 2009157623 Office Action dated 02/23/2010, 3 pages	☐
	43	JP 2009157623 Office Action dated 07/30/2010, 6 pages	☐
	44	JP 2009157623 Office Action response filed 06/18/2010, 37 pages (no translation)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

	45	JP 2009157623 request for accelerated exam filed 01/15/2010 (60 pages)	☐
	46	JP 2009157623 response filed 11/30/2010, 58 pages	☐
	47	Kay et al., "Congestive heart failure in pediatric patients," From the Department of Pediatrics, Duke University Medical Center, by Mosby, Inc., 6 pages (2001)	☐
	48	Kazerooni et al., "Cardiopulmonary Imaging," Lippincott Williams & Wilkins, pages 234-235 (2 pages) (2004)	☐
	49	Kieler-Jensen et al., "Inhaled nitric oxide in the evaluation of heart transplant candidates with elevated pulmonary vascular resistance", J. Heart Lung Transplant, Vol. 13, pages 366-375 (1994)	☐
	50	Kinsella et al., "Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory faliure: a randomised controlled trial," The Lancet, Vol. 354, pages 1061-1065 (1999)	☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	14454373
	Filing Date	2014-08-07
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-08
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	19820616
Application Number:	14454373
International Application Number:	
Confirmation Number:	3860
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
Filer:	Janis K. Fraser/Christine Grace
Filer Authorized By:	Janis K. Fraser
Attorney Docket Number:	26047-0003011
Receipt Date:	08-AUG-2014
Filing Date:	
Time Stamp:	17:21:07
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	IDS.pdf	62554 ba207e52261bff433c230efd9e6a371518e8d73b	no	1

Warnings:	
Information:	

2	Information Disclosure Statement (IDS) Form (SB08)	SB08.pdf	615442 d5cf7403b8b8980e728df271fab73abe0aaeedf4	no	8

Warnings:

Information:

A U.S. Patent Number Citation or a U.S. Publication Number Citation is required in the Information Disclosure Statement (IDS) form for autoloading of data into USPTO systems. You may remove the form to add the required data in order to correct the Informational Message if you are citing U.S. References. If you chose not to include U.S. References, the image of the form will be processed and be made available within the Image File Wrapper (IFW) system. However, no data will be extracted from this form. Any additional data such as Foreign Patent Documents or Non Patent Literature will be manually reviewed and keyed into USPTO systems.

Total Files Size (in bytes):	677996

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre	Conf. No.	: 3860
Serial No.	:	14/454,373		
Filed	:	August 7, 2014		
Title	:	METHODS FOR TREATING PATIENTS WHO ARE CANDIDATES FOR INHALED NITRIC OXIDE TREATMENT		

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SECOND INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing date of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in the prior applications and therefore are not provided in this application.

This statement is being filed within three months of the filing date of the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 8, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

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August 7, 2014

Attorney Docket No.: 26047-0003011 / 3000-US-0008CON8

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Presented for filing is a new continuation patent application for prioritized examination of:

Inventor: JAMES S. BALDASSARRE

Title: METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

This application claims the benefit of priority to the following applications:

Application No.	Country	Filing Date (MM/DD/YYYY)
12/494,598	United States	06/30/2009
12/820,866	United States	06/22/2010
12/821,041	United States	06/22/2010
13/651,660	United States	10/15/2012
13/683,417	United States	11/21/2012
13/683,444	United States	11/21/2012
14/451,057	United States	08/04/2014

Enclosed are the following papers, including those required to receive a filing date under 37 C.F.R. § 1.53(b):

	Pages
Specification	22
Claims	6
Abstract	1
Declaration (with cover page)	2

FISH.
FISH & RICHARDSON

Commissioner for Patents
August 7, 2014

Enclosures:

— Application Data Sheet, 8 pages.
— New disclosure information, including:
SB-08 (10 pages);
Information Disclosure Statement (2 pages)
— Power of Attorney, 3 pages.
— Certification and Request for Prioritized Examination (Track I), 1 page

Applicant claims small entity status. See 37 CFR 1.27.

Basic Filing Fee			$70
Search Fee			$300
Examination Fee			$360
Publication fee			$0
Track I processing fee			$70
Track I prioritized examination fee			$2000
Total Claims 20	over 20	**0 x $80**	$0
Independent Claims 3	over 3	**0 x $420**	$0
Fee for Multiple Dependent claims			$0
Application size fee for each 50 pages over 100 Total Sheets: 42x .75 - 100/50 = 0x			$0
Total Filing fee			$2800

The filing fee totaling $2800 is being paid on the Electronic Filing System (EFS) by way of Deposit Account authorization.

If this application is found to be incomplete, or if a telephone conference would otherwise be helpful, please call the undersigned at (617) 542-5070.

FISH.
FISH & RICHARDSON

Commissioner for Patents
August 7, 2014

Direct all correspondence to the following:

94169
PTO Customer Number

Respectfully submitted,

/Janis K. Fraser/

Janis K. Fraser, Ph.D., J.D.

Reg. No. 34,819
Enclosures
JKF/cng
23270585.doc

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Inventor Information:

Inventor 1 Remove

Legal Name

Prefix	Given Name	Middle Name	Family Name	Suffix
	James	S.	Baldassarre	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Doylestown	State/Province	PA	Country of Residence i	US

Mailing Address of Inventor:

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Address 2			
City	Doylestown	State/Province	PA
Postal Code	18901	Country i	US

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	94169		
Email Address	apsi@fr.com	Add Email	Remove Email

Application Information:

Title of the Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension		
Attorney Docket Number	26047-0003011	Small Entity Status Claimed	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Total Number of Drawing Sheets (if any)		Suggested Figure for Publication (if any)	

Filing By Reference :

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	94169		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.
When referring to the current application, please leave the application number blank.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Continuation of	14/451057	2014-08-04

Prior Application Status	Patented				Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14/451057	Continuation of	13/683417	2012-11-21	8795741	2014-08-05

Prior Application Status	Abandoned	Remove

PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/683417	Continuation of	12/820866	2010-06-22
Prior Application Status	Abandoned		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/820866	Continuation of	12/494598	2009-06-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/683417	Continuation of	13/651660	2012-10-15	8431163	2013-04-30
Prior Application Status	Patented				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/651660	Continuation of	12/821041	2010-06-22	8293284	2012-10-23
Prior Application Status	Abandoned				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/821041	Continuation of	12/494598	2009-06-30
Prior Application Status	Pending		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
14/451057	Division of	13/683444	2012-11-21
Prior Application Status	Abandoned		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/683444	Division of	12/820866	2010-06-22
Prior Application Status	Abandoned		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/820866	Continuation of	12/494598	2009-06-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/683444	Division of	13/651660	2012-10-15	8431163	2013-04-30
Prior Application Status	Patented				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/651660	Continuation of	12/821041	2010-06-22	8293284	2012-10-23
Prior Application Status	Abandoned				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/821041	Continuation of	12/494598	2009-06-30
Prior Application Status	Pending		Remove

PTO/AIA/14 (12-13)
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U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
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Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	13/683444	2012-11-21
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
13/683444	Division of	12/820866	2010-06-22
Prior Application Status	Abandoned		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/820866	Continuation of	12/494598	2009-06-30
Prior Application Status	Patented		Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/683444	Division of	13/651660	2012-10-15	8431163	2013-04-30
Prior Application Status	Patented				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13/651660	Continuation of	12/821041	2010-06-22	8293284	2012-10-23
Prior Application Status	Abandoned				Remove

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
12/821041	Continuation of	12/494598	2009-06-30

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button. Add

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(d). When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) [i] the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(h)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

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Application Number	Country [i]	Filing Date (YYYY-MM-DD)	Access Code [j] (if applicable)

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PTO/AIA/14 (12-13)
Approved for use through 01/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

☐ This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.
NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Authorization to Permit Access:

☐ Authorization to Permit Access to the Instant Application by the Participating Offices

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In accordance with 37 CFR 1.14(h)(3), access will be provided to a copy of the instant patent application with respect to: 1) the instant patent application-as-filed; 2) any foreign application to which the instant patent application claims priority under 35 U.S.C. 119(a)-(d) if a copy of the foreign application that satisfies the certified copy requirement of 37 CFR 1.55 has been filed in the instant patent application; and 3) any U.S. application-as-filed from which benefit is sought in the instant patent application.

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PTO/AIA/14 (12-13)
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
	Application Number	
Title of Invention	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension	

Applicant 1 Remove

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

Clear

◉ Assignee	○ Legal Representative under 35 U.S.C. 117	○ Joint Inventor
○ Person to whom the inventor is obligated to assign.	○ Person who shows sufficient proprietary interest	

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor :

If the Applicant is an Organization check here. ☒

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Email Address			

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Assignee Information including Non-Applicant Assignee Information:

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Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication . An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.

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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	26047-0003011
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Organization Name	INO Therapeutics LLC

Mailing Address Information For Assignee including Non-Applicant Assignee:

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Country i	US	Postal Code	08827
Phone Number		Fax Number	
Email Address			

Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button. Add

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Signature	/Janis Fraser/			Date (YYYY-MM-DD)	2014-08-07
First Name	Janis	Last Name	Fraser	Registration Number	34819

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METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] Not applicable.

STATEMENT CONCERNING GOVERNMENT INTEREST

[0002] Not applicable.

BACKGROUND OF THE INVENTION

[0003] INOmax®, (nitric oxide) for inhalation is an approved drug product for the treatment of term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension.

[0004] The use of inhaled NO (iNO) has been studied and reported in the literature. (Kieler-Jensen M et al., 1994, Inhaled Nitric Oxide in the Evaluation of Heart Transplant Candidates with Elevated Pulmonary Vascular Resistance, *J Heart Lung Transplantation* 13:366-375; Pearl RG et al., 1983, Acute Hemodynamic Effects of Nitroglycerin in Pulmonary Hypertension, *American College of Physicians* 99:9-13; Ajami GH et al., 2007, Comparison of the Effectiveness of Oral Sildenafil Versus Oxygen Administration as a Test for Feasibility of Operation for Patients with Secondary Pulmonary Arterial Hypertension, *Pediatr Cardiol*; Schulze-Neick I et al., 2003, Intravenous Sildenafil Is a Potent Pulmonary Vasodilator in Children With Congenital Heart Disease, *Circulation* 108(Suppl II):II-167-II-173; Lepore JJ et al., 2002, Effect of Sildenafil on the Acute Pulmonary Vasodilator Response to Inhaled Nitric Oxide in Adults with Primary Pulmonary Hypertension, *The American Journal of Cardiology* 90:677-680; and Ziegler JW et al., 1998, Effects of Dipyridamole and Inhaled Nitric Oxide in Pediatric Patients with Pulmonary Hypertension, *American Journal of Respiratory and Critical Care Medicine* 158:1388-95).

SUMMARY OF THE INVENTION

[0005] One aspect of the invention relates to a pre-screening methodology or protocol having exclusionary criteria to be evaluated by a medical provider prior to treatment of a patient with iNO. One objective of the invention is to evaluate and possibly exclude from treatment patients eligible for treatment with iNO, who have pre-existing left ventricular dysfunction (LVD). Patients who have pre-existing LVD may experience, and are at risk of, an increased rate of adverse events or serious adverse events (e.g., pulmonary edema) when treated with iNO. Such patients may be characterized as having a pulmonary capillary wedge pressure (PCWP) greater than 20 mm Hg, and should be evaluated on a case-by-case basis with respect to the benefit versus risk of using iNO as a treatment option.

[0006] Accordingly, one aspect of the invention includes a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b) informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or the serious adverse event associated with said medical treatment.

[0007] Further provided herein is a method of reducing the risk or preventing the occurrence, in a human patient, of an adverse event or a serious adverse event associated with a medical treatment comprising inhalation of nitric oxide, said method comprising the steps or acts of (a.) providing pharmaceutically acceptable nitric oxide gas to a medical provider; and, (b.) informing the medical provider that human patients having pre-existing left ventricular dysfunction experience an increased risk of serious adverse events associated with said medical treatment.

[0008] Another aspect of the invention is a method of reducing one or more of an AE or a SAE in an intended patient population in need of being treated with iNO comprising the steps or acts of (a.) identifying a patient eligible for iNO treatment; (b) evaluating and screening the patient to identify if the patient has pre-existing LVD, and (c) excluding from iNO treatment a patient identified as having pre-existing LVD.

[0009] Another aspect of the invention is a method of reducing the risk or preventing the occurrence, in a patient, of one or more of an AE or a SAE associated with a medical treatment comprising iNO, the method comprising the steps or acts of (a.) identifying a patient in need of receiving iNO treatment; (b.) evaluating and screening the patient to identify if the patient has pre-existing LVD; and (c.)administering iNO if the patient does not have pre-existing LVD, thereby reducing the risk or preventing the occurrence of the AE or the SAE associated with the iNO treatment. Alternatively, step (c) may comprise further evaluating the risk versus benefit of utilizing iNO in a patient where the patients has clinically significant LVD before administering iNO to the patient.

[0010] In an exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxides in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

[0011] In another exemplary embodiment of the method, the method further comprises informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

[0012] In an exemplary embodiment of the methods described herein, a patient having pre-existing LVD is characterized as having PCWP greater than 20 mm Hg.

[0013] In an exemplary embodiment of the method, the patients having pre-existing LVD demonstrate a PCWP $\geq$ 20 mm Hg.

[0014] In another exemplary embodiment of the method, the iNO treatment further comprises inhalation of oxygen (O_2) or concurrent ventilation.

[0015] In another exemplary embodiment of the method, the patients having pre-existing LVD have one or more of diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, or, associations thereof.

[0016] In another exemplary embodiment of the method, the patient population comprises children.

[0017] In another exemplary embodiment of the method, the patient population comprises adults.

[0018] In another exemplary embodiment of the method, the patients who have pre-existing LVD are at risk of experiencing and increased rate of one or more AEs or SAEs selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia, bradycardia or associations thereof.

[0019] In another exemplary embodiment of the method, the intended patient population in need of being treated with inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by a mean pulmonary artery pressure (PAPm) > 25 mm Hg at rest, PCWP $\leq$ 15 mm Hg, and, a pulmonary vascular resistance index (PVRI) > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; or, the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilatation testing.

[0020] In another exemplary embodiment of any of the above methods, the method further comprises reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient. The left ventricular afterload may be minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient. The left ventricular afterload may also be minimized or reduced using an intra-aortic balloon pump.

DETAILED DESCRIPTION OF THE EXEMPLARY EMBODIMENTS

[0021] INOmax® (nitric oxide) for inhalation was approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in 1999. Nitric oxide, the active substance in INOmax®, is a selective pulmonary vasodilator that increases the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from the lung regions with low ventilation/perfusion (V/Q) ratios toward regions with normal ratios. INOmax® significantly improves oxygenation, reduces the need for extracorporeal oxygenation and is indicated to be used in conjunction with ventilatory support and other appropriate agents. The current FDA-approved prescribing information for INOmax® is incorporated herein by reference in its entirety.

[0022] INOmax® is a gaseous blend of NO and nitrogen (0.08% and 99.92% respectively for 800 ppm; and 0.01% and 99.99% respectively for 100 ppm) and is supplied in aluminium cylinders as a compressed gas under high pressure. In general, INOmax® is administered to a patient in conjunction with ventilatory support and O_2. Delivery devices suitable for the safe and effective delivery of gaseous NO for inhalation include the INOvent®, INOmax DS®, INOpulse®, INOblender®, or other suitable drug delivery and regulation devices or components incorporated therein, or other related processes, which are described in various patent documents including USPNs 5,558,083; 5,732,693; 5,752,504; 5,732,694; 6,089,229; 6,109,260; 6,125,846; 6,164,276; 6,581,592; 5,918,596; 5,839,433; 7,114,510; 5,417;950; 5,670,125; 5,670,127; 5,692,495; 5,514,204; 7,523,752; 5,699,790; 5,885,621; US Patent Application Serial Nos. 11/355,670 (US 2007/0190184); 10/520,270 (US 2006/0093681); 11/401,722 (US 2007/0202083); 10/053,535 (US 2002/0155166); 10/367,277 (US 2003/0219496); 10/439,632 (US 2004/0052866); 10/371,666 (US 2003/0219497); 10/413,817 (US 2004/0005367); 12/050,826 (US 2008/0167609); and PCT/US2009/045266, all of which are incorporated herein by reference in their entirety.

[0023] Such devices deliver INOmax® into the inspiratory limb of the patient breathing circuit in a way that provides a constant concentration of NO to the patient throughout the inspired breath. Importantly, suitable delivery devices provide continuous integrated monitoring of inspired O_2, NO_2 and NO, a comprehensive alarm system, a suitable power source for uninterrupted NO delivery and a backup NO delivery capability.

[0024] As used herein, the term "children" (and variations thereof) includes those being around 4 weeks to 18 years of age.

[0025] As used herein, the term "adult" (and variations thereof) includes those being over 18 years of age.

[0026] As used herein, the terms "adverse event" or "AE" (and variations thereof) mean any untoward occurrence in a subject, or clinical investigation subject administered a pharmaceutical product (such as nitric oxide) and which does not necessarily have a causal relationship with such treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal/investigational product, whether or not related to the

investigational product. A relationship to the investigational product is not necessarily proven or implied. However, abnormal values are not reported as adverse events unless considered clinically significant by the investigator.

[0027] As used herein, the terms "adverse drug reaction" or "ADR" (and variations thereof) mean any noxious and unintended response to a medicinal product related to any dose.

[0028] As used herein, the terms "serious adverse event" or "SAE" (or "serious adverse drug reaction" or "serious ADR") (and variations thereof) mean a significant hazard or side effect, regardless of the investigator's opinion on the relationship to the investigational product. A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death; is life-threatening (which refers to an event/reaction where the patient was at risk of death at the time of the event/reaction, however this does not refer to an event/reaction that hypothetically may have caused death if it were more severe); requires inpatient hospitalization or results in prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; or, is a medically important event or reaction. Medical and scientific judgment is exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above--these are also considered serious. Examples of such medical events include cancer, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalizations, or the development of drug dependency or drug abuse. Serious clinical laboratory abnormalities directly associated with relevant clinical signs or symptoms are also reported.

[0029] Left Ventricular Dysfunction. Patients having pre-existing LVD may be described in general as those with elevated pulmonary capillary wedge pressure, including those with diastolic dysfunction (including hypertensive cardiomyopathy), those with systolic dysfunction, including those with cardiomyopathies (including ischemic or viral cardiomyopathy, or idiopathic cardiomyopathy, or autoimmune disease related cardiomyopathy, and side effects due to drug related or toxic-related cardiomyopathy), or structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension,

pulmonary hypertension and cardiomyopathy, or associations thereof. Identifying patients with pre-existing LVD is known to those skilled in the medicinal arts, and such techniques for example may include assessment of clinical signs and symptoms of heart failure, or echocardiography diagnostic screening.

[0030] Pulmonary Capillary Wedge Pressure. Pulmonary capillary wedge pressure, or "PCWP", provides an estimate of left atrial pressure. Identifying patients with pre-existing PCWP is known to those skilled in the medicinal arts, and such techniques for example may include measure by inserting balloon-tipped, multi-lumen catheter (also known as a Swan-Ganz catheter). Measure of PCWP may be used as a means to diagnose the severity of LVD (sometimes also referred to as left ventricular failure). PCWP is also a desired measure when evaluating pulmonary hypertension. Pulmonary hypertension is often caused by an increase in pulmonary vascular resistance (PVR), but may also arise from increases in pulmonary venous pressure and pulmonary blood volume secondary to left ventricular failure or mitral or aortic valve disease.

[0031] In cardiac physiology, afterload is used to mean the tension produced by a chamber of the heart in order to contract. If the chamber is not mentioned, it is usually assumed to be the left ventricle. However, the strict definition of the term relates to the properties of a single cardiac myocyte. It is therefore only of direct relevance in the laboratory; in the clinic, the term end-systolic pressure is usually more appropriate, although not equivalent.

[0032] The terms "left ventricular afterload" (and variations thereof) refer to the pressure that the chamber of the heart has to generate in order to eject blood out of the chamber. Thus, it is a consequence of the aortic pressure since the pressure in the ventricle must be greater than the systemic pressure in order to open the aortic valve. Everything else held equal, as afterload increases, cardiac output decreases. Disease processes that increase the left ventricular afterload include increased blood pressure and aortic valve disease. Hypertension (Increased blood pressure) increases the left ventricular afterload because the left ventricle has to work harder to eject blood into the aorta. This is because the aortic valve won't open until the pressure generated in the left ventricle is higher than the elevated blood pressure. Aortic stenosis increases the afterload because the left ventricle has to overcome the pressure gradient caused by the stenotic aortic valve in addition to the blood pressure in order to eject blood into the

aorta. For instance, if the blood pressure is 120/80, and the aortic valve stenosis creates a trans-valvular gradient of 30 mmHg, the left ventricle has to generate a pressure of 110 mmHg in order to open the aortic valve and eject blood into the aorta. Aortic insufficiency increases afterload because a percentage of the blood that is ejected forward regurgitates back through the diseased aortic valve. This leads to elevated systolic blood pressure. The diastolic blood pressure would fall, due to regurgitation. This would result in an increase pulse pressure. Mitral regurgitation decreases the afterload. During ventricular systole, the blood can regurgitate through the diseased mitral valve as well as be ejected through the aortic valve. This means that the left ventricle has to work less to eject blood, causing a decreased afterload. Afterload is largely dependent upon aortic pressure.

[0033] An intra-aortic balloon pump (IABP) is a mechanical device that is used to decrease myocardial oxygen demand while at the same time increasing cardiac output. By increasing cardiac output it also increases coronary blood flow and therefore myocardial oxygen delivery. It consists of a cylindrical balloon that sits in the aorta and counterpulsates. That is, it actively deflates in systole increasing forward blood flow by reducing afterload thus, and actively inflates in diastole increasing blood flow to the coronary arteries. These actions have the combined result of decreasing myocardial oxygen demand and increasing myocardial oxygen supply. The balloon is inflated during diastole by a computer controlled mechanism, usually linked to either an ECG or a pressure transducer at the distal tip of the catheter; some IABPs, such as the Datascope System 98XT, allow for asynchronous counterpulsation at a set rate, though this setting is rarely used. The computer controls the flow of helium from a cylinder into and out of the balloon. Helium is used because its low viscosity allows it to travel quickly through the long connecting tubes, and has a lower risk of causing a harmful embolism should the balloon rupture while in use. Intraaortic balloon counterpulsation is used in situations when the heart's own cardiac output is insufficient to meet the oxygenation demands of the body. These situations could include cardiogenic shock, severe septic shock, post cardiac surgery and numerous other situations.

[0034] Patients eligible for treatment with iNO. In general, patients approved for treatment of iNO are term and near-term (>34 weeks gestation) neonates having hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension, a condition also known as persistent pulmonary hypertension in the newborn

(PPHN). Due to the selective, non-systemic nature of iNO to reduce pulmonary hypertension, physicians skilled in the art further employ INOmax® to treat or prevent pulmonary hypertension and improve blood O_2 levels in a variety of other clinical settings, including in both pediatric and adult patients suffering from acute respiratory distress syndrome (ARDS), pediatric and adult patients undergoing cardiac or transplant surgeries, pediatric and adult patients for testing to diagnose reversible pulmonary hypertension, and in pediatric patients with congenital diaphragmatic hernia. In most, if not all, of these applications, INOmax® acts by preventing or treating reversible pulmonary vasoconstriction, reducing pulmonary arterial pressure and improving pulmonary gas exchange.

[0035] A small proportion of INOmax® sales stem from its use by clinicians in a premature infant population. In these patients, INOmax® is generally utilized by physicians as a rescue therapy primarily to vasodilate the lungs and improve pulmonary gas exchange. Some physicians speculate that INOmax® therapy may promote lung development and/or reduce or prevent the future development of lung disease in a subset of these patients. Although the precise mechanism(s) responsible for the benefits of INOmax® therapy in these patients is not completely understood, it appears that the benefits achieved in at least a majority of these patients are due to the ability of INOmax® to treat or prevent reversible pulmonary vasoconstriction.

[0036] In clinical practice, the use of INOmax® has reduced or eliminated the use of high risk systemic vasodilators for the treatment of PPHN. INOmax®, in contrast to systemic vasodilators, specifically dilates the pulmonary vasculature without dilating systemic blood vessels. Further, iNO preferentially vasodilates vessels of aveoli that are aerated, thus improving V/Q matching. In contrast, systemic vasodilators may increase blood flow to atelectatic (deflated or collapsed) alveoli, thereby increasing V/Q mismatch and worsening arterial oxygenation. (*See* Rubin LJ, Kerr KM, Pulmonary Hypertension, in *Critical Care Medicine: Principles of Diagnosis and Management in the Adult, 2d Ed.*, Parillo JE, Dellinger RP (eds.), Mosby, Inc. 2001, pp. 900-09 at 906; Kinsella JP, Abman SH, The Role of Inhaled Nitric Oxide in Persistent Pulmonary Hypertension of the Newborn, in *Acute Respiratory Care of the Neonate: A Self-Study Course, 2d Ed.*, Askin DF (ed.), NICU Ink Book Publishers, 1997, pp. 369-378 at 372-73).

[0037] INOmax® also possesses highly desirable pharmacokinetic properties as a lung-specific vasodilator when compared to other ostensibly "pulmonary-specific vasodilators." For example, the short half-life of INOmax® allows INOmax® to exhibit rapid "on" and "off" responses relative to INOmax® dosing, in contrast to non-gaseous alternatives. In this way, INOmax® can provide physicians with a useful therapeutic tool to easily control the magnitude and duration of the pulmonary vasodilatation desired. Also, the nearly instantaneous inactivation of INOmax® in the blood significantly reduces or prevents vasodilatation of non-pulmonary vessels.

[0038] The pivotal trials leading to the approval of INOmax® were the CINRGI and NINOS study.

[0039] CINRGI study. (See Davidson et al., March 1998, Inhaled Nitric Oxide for the Early Treatment of Persistent Pulmonary Hypertension of the term Newborn; A Randomized, Double-Masked, Placebo-Controlled, Dose-Response, Multicenter Study; *PEDIATRICS* Vol. 101, No. 3, p. 325).

[0040] This study was a double-blind, randomized, placebo-controlled, multicenter trial of 186 term and near-term neonates with pulmonary hypertension and hypoxic respiratory failure. The primary objective of the study was to determine whether INOmax® would reduce the receipt of extracorporeal membrane oxygenation (ECMO) in these patients. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS) (35%), idiopathic persistent pulmonary hypertension of the newborn (PPHN) (30%), pneumonia/sepsis (24%), or respiratory distress syndrome (RDS) (8%). Patients with a mean PaO_2 of 54 mm Hg and a mean oxygenation index (OI) of 44 cm H_2O/mm Hg were randomly assigned to receive either 20 ppm INOmax® (n=97) or nitrogen gas (placebo; n=89) in addition to their ventilatory support. Patients that exhibited a $PaO_2 > 60$ mm Hg and a pH < 7.55 were weaned to 5 ppm INOmax® or placebo. The primary results from the CINRGI study are presented in Table 4. ECMO was the primary endpoint of the study.

Table 1: Summary of Clinical Results from CINRGI Study

	Placebo	INOmax®	P value
Death or ECMO	51/89 (57%)	30/97 (31%)	<0.001
Death	5/89 (6%)	3/97 (3%)	0.48

[0041] Significantly fewer neonates in the ECMO group required ECMO, and INOmax® significantly improved oxygenation, as measured by PaO_2, OI, and alveolar-arterial gradient.

[0042] NINOS study. (See Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure; NEJM, Vol. 336, No. 9, 597).

[0043] The Neonatal Inhaled Nitric Oxide Study (NINOS) group conducted a double-blind, randomized, placebo-controlled, multicenter trial in 235 neonates with hypoxic respiratory failure. The objective of the study was to determine whether iNO would reduce the occurrence of death and/or initiation of ECMO in a prospectively defined cohort of term or near-term neonates with hypoxic respiratory failure unresponsive to conventional therapy. Hypoxic respiratory failure was caused by meconium aspiration syndrome (MAS; 49%), pneumonia/sepsis (21%), idiopathic primary pulmonary hypertension of the newborn (PPHN; 17%), or respiratory distress syndrome (RDS; 11%). Infants ≤ 14 days of age (mean, 1.7 days) with a mean PaO_2 of 46 mm Hg and a mean oxygenation index (OI) of 43 cm H_2O/mmHg were initially randomized to receive 100% O_2 with (n=114) or without (n=121) 20 ppm NO for up to 14 days. Response to study drug was defined as a change from baseline in PaO_2 30 minutes after starting treatment (full response = > 20 mmHg, partial = 10–20 mm Hg, no response = < 10 mm Hg). Neonates with a less than full response were evaluated for a response to 80 ppm NO or control gas. The primary results from the NINOS study are presented in Table 2.

Table 2: Summary of Clinical Results from NINOS Study

	Control (n=121)	NO (n=114)	P value
Death or ECMO*, †	77 (64%)	52 (46%)	0.006
Death	20 (17%)	16 (14%)	0.60
ECMO	66 (55%)	44 (39%)	0.014

* Extracorporeal membrane oxygenation
† Death or need for ECMO was the study's primary end point

[0044] Adverse Events from CINRGI & NINOS. Controlled studies have included 325 patients on INOmax® doses of 5 to 80 ppm and 251 patients on placebo. Total mortality in the pooled trials was 11% on placebo and 9% on INOmax®, a result adequate to exclude INOmax® mortality being more than 40% worse than placebo.

[0045] In both the NINOS and CINRGI studies, the duration of hospitalization was similar in INOmax® and placebo-treated groups.

[0046] From all controlled studies, at least 6 months of follow-up is available for 278 patients who received INOmax® and 212 patients who received placebo. Among these patients, there was no evidence of an AE of treatment on the need for re-hospitalization, special medical services, pulmonary disease, or neurological squeal.

[0047] In the NINOS study, treatment groups were similar with respect to the incidence and severity of intracranial hemorrhage, Grade IV hemorrhage, per ventricular leukomalacia, cerebral infarction, seizures requiring anticonvulsant therapy, pulmonary hemorrhage, or gastrointestinal hemorrhage.

[0048] The table below shows adverse reactions that occurred in at least 5% of patients receiving INOmax® in the CINRGI study. None of the differences in these adverse reactions were statistically significant when iNO patients were compared to patients receiving placebo.

Table 3: ADVERSE REACTIONS ON THE CINRGI TRIAL

Adverse Reaction	Placebo (n=89)	Inhaled NO (n=97)
Atelectasis	5 (4.8%)	7 (6.5%)
Bilirubinemia	6 (5.8%)	7 (6.5%)
Hypokalemia	5 (4.8%)	9 (8.3%)
Hypotension	3 (2.9%)	6 (5.6%)
Thrombocytopenia	20 (19.2%)	16 (14.8%)

[0049] Post-Marketing Experience. The following AEs have been reported as part of the post-marketing surveillance. These events have not been reported above. Given the nature of spontaneously reported post-marketing surveillance data, it is impossible to determine the actual incidence of the events or definitively establish their causal relationship to the drug. The listing is alphabetical: dose errors associated with the delivery system; headaches associated with environmental exposure of INOmax® in hospital staff; hypotension associated with acute withdrawal of the drug; hypoxemia associated with acute withdrawal of the drug; pulmonary edema in patients with CREST syndrome.

[0050] An analysis of AEs and SAEs from both the CINRGI and NINOS studies, in addition to post-marketing surveillance, did not suggest that patients who have pre-existing LVD could experience an increased risk of AEs or SAEs. Nor was it predictable to physicians skilled in the art that patients having pre-existing LVD (possibly identified as those patients having a PCWP greater than 20 mmHg) should be evaluated in view of the benefit versus risk of using iNO in patients with clinically significant LVD, and that these patients should be evaluated on a case by case basis.

EXAMPLE 1: INOT22 STUDY

[0051] The INOT22, entitled "Comparison of supplemental oxygen and nitric oxide for inhalation plus oxygen in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilatory testing" was conducted both to access the safety and effectiveness

of INOmax® as a diagnostic agent in patients undergoing assessment of pulmonary hypertension (primary endpoint), and to confirm the hypothesis that iNO is selective for the pulmonary vasculature (secondary endpoint).

[0052] During, and upon final analysis of the INOT22 study results, applicants discovered that rapidly decreasing the pulmonary vascular resistance, via the administration of iNO to a patient in need of such treatment, may be detrimental to patients with concomitant, pre-existing LVD. Therefore, a precaution for patients with LVD was proposed to be included in amended prescribing information for INOmax®. Physicians were further informed to consider reducing left ventricular afterload to minimize the occurrence of pulmonary edema in patients with pre-existing LVD.

[0053] In particular, the INOT22 protocol studied consecutive children undergoing cardiac catheterization that were prospectively enrolled at 16 centers in the US and Europe. Inclusion criteria: 4 weeks to 18 years of age, pulmonary hypertension diagnosis, i.e. either idiopathic pulmonary hypertension (IPAH) or related to congenital heart disease (CHD) (repaired or unrepaired) or cardiomyopathy, with pulmonary vascular resistance index (PVRI) > 3 u-m^2. Later amendments, as discussed herein, added an additional inclusionary criteria of a PCWP less than 20 gmm Hg. Patients were studied under general anaesthesia, or with conscious sedation, according to the practice of the investigator. Exclusion criteria: focal infiltrates on chest X-ray, history of intrinsic lung disease, and/or currently taking PDE-5 inhibitors, prostacyclin analogues or sodium nitroprusside. The study involved supplemental O_2 and NO for inhalation plus O_2 in the evaluation of the reactivity of the pulmonary vasculature during acute pulmonary vasodilator testing. Consecutive children undergoing cardiac catheterization were prospectively enrolled at 16 centers in the US and Europe. As hypotension is expected in these neonatal populations, the comparison between iNO and placebo groups is difficult to assess. A specific secondary endpoint was evaluated in study INOT22 to provide a more definitive evaluation.

[0054] The primary objective was to compare the response frequency with iNO and O_2 vs. O_2 alone; in addition, all subjects were studied with iNO alone. Patients were studied during five periods: Baseline 1, Treatment Period 1, Treatment Period 2, Baseline 2 and Treatment Period 3. All patients received all three treatments; treatment sequence was randomized by

center in blocks of 4; in Period 1, patients received either NO alone or O_2 alone, and the alternate treatment in Period 3. All patients received the iNO and O_2 combination treatment in Period 2. Once the sequence was assigned, treatment was unblinded. Each treatment was given for 10 minutes prior to obtaining hemodynamic measurements, and the Baseline Period 2 was at least 10 minutes.

[0055] Results for the intent-to-treat (ITT) population, defined as all patients who were randomized to receive drug, indicated that treatment with NO plus O_2 and O_2 alone significantly increased systemic vascular resistance index (SVRI) (Table 4). The change from baseline for NO plus O_2 was 1.4 Woods Units per meter^2 (WU·m^2) ($p = 0.007$) and that for O_2 was 1.3 WU·m^2 ($p = 0.004$). While the change from baseline in SVRI with NO alone was -0.2 WU·m^2 ($p = 0.899$) which demonstrates a lack of systemic effect.

Table 4: SVRI Change From Baseline by Treatment (Intent-to-Treat)

	Treatment		
SVRI ($WU \cdot m^2$)	**NO Plus O_2 (n=109)**	**O_2 (n=106)**	**NO (n=106)**
Baseline (room air)			
Mean	17.2	17.6	18.0
Standard Deviation (SD)	8.86	9.22	8.44
Median	15.9	16.1	16.2
Minimum, maximum	-7.6, 55.6	-7.6, 55.6	1.9, 44.8
Post-treatment			
Mean	18.7	18.9	17.8
SD	9.04	8.78	9.40
Median	17.1	17.1	15.4
Minimum, maximum	3.0, 47.4	3.9, 43.6	3.3, 50.7
Change From Baseline			
Mean	1.4	1.3	-0.2
SD	5.94	5.16	4.65
Median	1.2	1.0	0.2
Minimum, maximum	-20.5, 19.1	-18.1, 17.7	-12.5, 12.7
p-value[a]	0.007	0.004	0.899
Pairwise comparisons NO plus O_2 versus O_2, p=0.952 NO plus O_2 versus NO, p=0.014 O_2 versus NO, p=0.017			

[a] p-value from a Wilcoxon Signed Rank Test. Only patients with data to determine response at both treatments are included in this analysis.

Source: INOT22 CSR Table 6.4.1 and Appendix 16.2.6 (ATTACHMENT 1)

[0056] The ideal pulmonary vasodilator should reduce PVRI and/or PAPm while having no appreciable effect on systemic blood pressure or SVRI. In this case, the ratio of PVRI to SVRI would decrease, given some measure of the selectivity of the agent for the pulmonary vascular bed. The change in the ratio of PVRI to SVRI by treatment is shown in Table 5.

Table 5: Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Change from Baseline			
Mean	-0.2	-0.1	-0.1
SD	0.52	0.31	0.54
Median	-0.1	-0.1	0.0
Minimum, Maximum	-4.4, 2.0	-1.6, 2.0	-4.4, 1.6
P Value[1]	< 0.001	< 0.001	0.002

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.1 (ATTACHMENT 2)

[0057] All three treatments have a preferential effect on the pulmonary vascular bed, suggesting that all three are selective pulmonary vasodilators. The greatest reduction in the ratio was during treatment with NO plus O_2, possibly due to the decrease in SVRI effects seen with O_2 and NO plus O_2. These results are displayed as percent change in the ratio (See Table 6).

Table 6: Percent Change in Ratio of PVRI to SVRI by Treatment (Intent-to-Treat)

	Treatment		
Ratio PVRI/SVRI	**NO Plus O_2 (n=108)**	**O_2 (n=105)**	**NO (n=106)**
Baseline			
Mean	0.6	0.5	0.6
SD	0.60	0.45	0.56
Median	0.5	0.5	0.4
Minimum, Maximum	-1.6, 4.7	-1.6, 1.8	0.0, 4.7
Post Treatment			
Mean	0.4	0.4	0.5
SD	0.31	0.31	0.46
Median	0.3	0.4	0.3
Minimum, Maximum	0.0, 1.3	0.0, 1.4	-1.2, 2.2
Percent Change from Baseline			
Mean	-33.5	-19.3	-6.2
SD	36.11	34.59	64.04
Median	-34.0	-21.3	-13.8
Minimum, Maximum	-122.2, 140.1	-122.7, 93.3	-256.1, 294.1
P Value[1]	< 0.001	< 0.001	0.006

[1] Wilcoxon Signed Rank Test
Source: INOT22 CSR Table 6.5.2 (ATTACHMENT 3)

[0058] NO plus O_2 appeared to provide the greatest reduction in the ratio, suggesting that NO plus O_2 was more selective for the pulmonary vasculature than either agent alone.

[0059] Overview of Cardiovascular Safety. In the INOT22 diagnostic study, all treatments (NO plus O_2, O_2, and NO) were well-tolerated. Seven patients of 134 treated experienced an AE during the study. These included cardiac arrest, bradycardia, low cardiac output (CO) syndrome, elevated ST segment (the portion of an electrocardiogram between the end of the QRS complex and the beginning of the T wave) on the electrocardiography (ECG)

decreased O_2 saturation, hypotension, mouth hemorrhage and pulmonary hypertension (PH). The numbers of patients and events were too small to determine whether risk for AEs differed by treatment, diagnosis, age, gender or race. Eight patients are shown in Table 5 due to the time period in which events are reported. AEs were reported for 12 hours or until hospital discharge (which limits the period in which such events can be reported). There is technically no time limit in which SAEs are to be reported. So, there were 7 AEs during the study and at least one SAE after the study.

[0060] A total of 4 patients had AEs assessed as being related to study drug. These events included bradycardia, low CO syndrome, ST segment elevation on the ECG, low O_2 saturation, PH and hypotension. All but 2 AEs were mild or moderate in intensity and were resolved. Study treatments had slight and non-clinically significant effects on vital signs including heart rate, systolic arterial pressure and diastolic arterial pressure. When an investigator records an AE, they are required to say if (in their opinion) the event is related to the treatment or not. In this case, 4 of 7 were considered by the investigator to be related to treatment.

[0061] The upper limit of normal PCWP in children is 10-12 mm Hg and 15 mm Hg in adults. In INOT22, a baseline PCWP value was not included as exclusion criteria. However, after the surprising and unexpected identification of SAEs in the early tested patients, it was determined that patients with pre-existing LVD had an increased risk of experiencing an AE or SAE upon administration (e.g., worsening of left ventricular function due to the increased flow of blood through the lungs). Accordingly, the protocol for INOT22 was thereafter amended to exclude patients with a baseline PCWP greater than 20 mm Hg after one patient experienced acute circulatory collapse and died during the study. The value "20 mm Hg" was selected to avoid enrollment of a pediatric population with LVD such that they would be most likely at-risk for these SAEs.

[0062] SAEs were collected from the start of study treatment until hospital discharge or 12 hours, whichever occurred sooner. Three SAEs were reported during the study period, and a total of 7 SAEs were reported. Three of these were fatal SAEs and 4 were nonfatal (one of which led to study discontinuation). In addition, one non-serious AE also lead to

discontinuation. A list of subjects who died, discontinued or experienced an SAE is provided in Table 5 below.

Table 5: Subjects that died, discontinued or experienced SAEs

Patient number	AE	Serious?	Fatal?	Discontinued treatment?
01020	Desaturation (hypoxia)	No	No	Yes
02002	Pulmonary edema	Yes	No	No
04001	Hypotension and cardiac arrest	Yes	Yes	No
04003	Hypotension and ECG changes	Yes	No	Yes
04008	Hypotension and hypoxemia	Yes	Yes	No
05002	Hypoxia and bradycardia (also pulmonary edema)	Yes	Yes	No
07003	Cardiac arrest	Yes	No	No
17001	Hypoxia	Yes	No	No

[0063] Two of the 3 fatal SAEs were deemed related to therapy. All 4 non-fatal SAEs were also considered related to therapy. The numbers of patients and events were too small to determine whether risk for SAEs differed by treatment, diagnosis, age, gender or race. At least two patients developed signs of pulmonary edema (subjects 05002 and 02002). This is of interest because pulmonary edema has previously been reported with the use of iNO in patients with LVD, and may be related to decreasing PVRI and overfilling of the left atrium. (Hayward CS et al., 1996, Inhaled Nitric Oxide in Cardiac Failure: Vascular Versus Ventricular Effects, *J Cardiovascular Pharmacology* 27:80-85; Bocchi EA et al., 1994, Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure, *Am J Cardiology* 74:70-72; and, Semigran MJ et al., 1994, Hemodynamic Effects of Inhaled Nitric Oxide in Heart Failure, *J Am Coll Cardiology* 24:982-988).

[0064] Although the SAE rate is within range for this population, it appears that patients with the most elevated PCWP at baseline had a disproportionately high number of these events. (Bocchi EA et al., 1994; Semigran MJ et al., 1994).

[0065] In the INOT22 study, 10 of the total 134 patients had a baseline PCWP $\geq$ 18 mm Hg (7.5%), of which, 3 subjects (04001, 02002 and 04003) had a SAE or were prematurely discontinued from the study (30%) compared to 6.5% for the entire cohort.

[0066] Although there were very few significant AEs in the INOT22 study, these events are consistent with the expected physiologic changes in patients with severe LVD. The events also corroborate prior observations that iNO is rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients. The actual incidence of acute LVD during acute ventricular failure (AVT) is unknown. However, it is reasonable to expect that a significant number of patients are at-risk for an increased incidence of SAEs upon iNO treatment based upon the nature of the underlying nature of the illness, i.e., pulmonary hypertension and cardiovascular disease more generally. Thus, it would be advantageous to have physicians identify these patients prior to beginning iNO treatment, so that the physicians are alerted to this possible outcome.

[0067] Benefits and Risks Conclusions. The INOT22 study was designed to demonstrate the physiologic effects of iNO in a well defined cohort of children (i.e., intended patient population) with pulmonary hypertension using a high concentration, 80 ppm, of iNO, i.e., one that would be expected to have the maximal pharmacodynamic effect. INOT22 was the largest and most rigorous pharmacodynamic study of iNO conducted to date, and it confirms a number of prior observations, such as iNO being rapidly acting, selective for the pulmonary vasculature, and well-tolerated in most patients.

[0068] It is also acknowledged that rapidly decreasing the PVR may be undesirable and even dangerous in patients with concomitant LVD. In the INOT22 study, the overall numbers of SAEs and fatal SAEs are within the expected range for patients with this degree of cardiopulmonary disease. The overall rate is 7/124 (5.6%), which is closely comparable to the rate of 6% recently reported in a very similar cohort of patients. (Taylor CJ et al., 2007, Risk of cardiac catheterization under anaesthesia in children with pulmonary hypertension, *Br J Anaesth* 98(5):657-61). Thus, the overall rate of SAEs would seem to be more closely related to the underlying severity of illness of the patients rather than to the treatments given during this study.

[0069] The INOT22 study results demonstrate that patients who had pre-existing LVD may experience an increased rate of SAEs (e.g., pulmonary edema). During the course of the study, the protocol was amended to exclude patients with a PCWP > 20 mmHg. The benefit/risk of using iNO in patients with clinically significant LVD should be evaluated on a case by case

basis. A reduction in left ventricular afterload may perhaps be applied to minimize the occurrence of pulmonary edema.

CLAIMS

We Claim:

1. A method of reducing one or more of an adverse event or a serious adverse event in an intended patient population in need of being treated with inhalation of nitric oxide comprising excluding from such treatment patients who have pre-existing left ventricular dysfunction.

2. The method of claim 1, wherein the patients further have a pulmonary capillary wedge pressure greater than 20 mm Hg.

3. The method of claim 1, wherein the treatment further comprises inhalation of oxygen .

4. The method of claim 1, wherein the treatment is delivered using a ventilator.

5. The method of claim 1, wherein the patients having pre-existing left ventricular dysfunction have one or more of a condition selected from diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy , drug-related cardiomyopathy, toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension and pulmonary hypertension cardiomyopathy, or associations thereof.

6. The method of any one of claims 1-5, wherein the patient population comprises children.

7. The method of any one of claims 1-5, wherein the patient population comprises adults.

8. The method of claim 1, wherein the patients are at risk of an adverse event or serious the adverse event is selected from pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia and bradycardia, or, associations thereof.

9. A method of reducing the risk or preventing the occurrence, in a human patient, of one or more of adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

a. identifying a human patient eligible for inhalation of nitric oxide treatment;

b. determining if said patient has pre-existing left ventricular dysfunction; and

c. administering said medical treatment if said patient does not have pre-existing left ventricular dysfunction;

thereby reducing the risk or preventing the occurrence of the adverse event or serious adverse event associated with said medical treatment.

10. The method of claim 9, wherein said patient further exhibits a pulmonary capillary wedge pressure greater than 20 mm Hg.

11. The method of claims 9 or 10, wherein the patients who have pre-existing left ventricular dysfunction have one or more conditions selected from diastolic dysfunction, hypertensive cardiomyopathy, systolic dysfunction, ischemic cardiomyopathy, viral cardiomyopathy, idiopathic cardiomyopathy, autoimmune disease related cardiomyopathy, side effects due to drug-related cardiomyopathy, side effects due to toxin-related cardiomyopathy, structural heart disease, valvular heart disease, congenital heart disease, idiopathic pulmonary arterial hypertension, pulmonary hypertension and cardiomyopathy, or associations thereof.

12. The method of claim 9, wherein the medical treatment further comprises inhalation of oxygen.

13. The method of claim 9, wherein the treatment is delivered using a ventilator.

14. The method of claim 9, wherein the patient is a child.

15. The method of claim 9, wherein the patient is an adult.

16. A method of reducing the risk or preventing the occurrence, in a human patient, of one or more adverse events or a serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

a. providing pharmaceutically acceptable nitric oxide gas to a medical provider; and,

b. informing the medical provider that excluding human patients who have pre-existing left ventricular dysfunction from said treatment reduces the risk or prevents the occurrence of the adverse event or serious adverse event associated with said medical treatment.

17. The method of claim 16, wherein the patient is a child.

18. The method of claim 16, wherein the patient is an adult.

19. The method of claim 16, wherein the adverse event or serious adverse event is one or more of pulmonary edema, hypotension, cardiac arrest, electrocardiogram changes, hypoxemia, hypoxia and bradycardia, or, associations thereof.

20. A method of reducing the risk or preventing the occurrence, in a human patient, of one or more of adverse events or a serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, said method comprising:

a. providing pharmaceutically acceptable nitric oxide gas to a medical provider; and,

b. informing the medical provider that human patients having preexisting left ventricular dysfunction experience an increased rate of serious adverse events associated with said medical treatment.

21. The method of claim 20, further comprising informing the medical provider of a risk of an adverse event or a serious adverse event in human patients who have a pulmonary capillary wedge pressure greater than 20 mm Hg.

22. The method of claim 20, further comprising informing the medical provider that there is a risk associated with using inhaled nitric oxides in human patients who have preexisting or clinically significant left ventricular dysfunction and that such risk should be evaluated on a case by case basis.

23. The method of claim 20, further comprising informing the medical provider that there is a risk associated with using inhaled nitric oxide in human patients who have left ventricular dysfunction.

24. A method of reducing one or more adverse events or serious adverse events in an intended patient population in need of being treated with iNO comprising:

a. identifying a patient eligible for iNO treatment;

b. evaluating and screening the patient to identify if the patient has pre-existing left ventricular dysfunction; and

c. excluding from iNO treatment a patient identified as having pre-existing left ventricular dysfunction.

25. A method of reducing the risk or preventing the occurrence, in a patient, of one or more adverse events or serious adverse events associated with a medical treatment comprising inhalation of nitric oxide, the method comprising:

a. identifying a patient in need of receiving inhalation of nitric oxide treatment;

b. evaluating and screening the patient to identify if the patient has pre-existing left ventricular dysfunction; and

c. administering the inhalation of nitric oxide if the patient does not have pre-existing left ventricular dysfunction, thereby reducing the risk or preventing the occurrence of the adverse event or significant adverse event associated with the inhalation of nitric oxide treatment.

26. The method of claims 24 or 25, wherein the patient having pre-existing left ventricular dysfunction exhibits a pulmonary capillary wedge pressure greater than 20 mm Hg.

27. The method of claim 1, wherein the intended patient population in need of being treated with the inhalation of nitric oxide has one or more of idiopathic pulmonary arterial hypertension characterized by PAPm > 25 mm Hg at rest, PCWP $\leq$ 15 mm Hg, and, a PVRI > 3 u·m^2; congenital heart disease with pulmonary hypertension repaired and unrepaired characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; cardiomyopathy characterized by PAPm > 25 mm Hg at rest and PVRI > 3 u·m^2; or, the patient is scheduled to undergo right heart catheterization to assess pulmonary vasoreactivity by acute pulmonary vasodilation testing.

28. The method of claim 1, 9, 16, 20, 24 or 25, further comprising reducing left ventricular afterload to minimize or reduce the risk of the occurrence of an adverse event or serious adverse event being pulmonary edema in the patient.

29. The method of claim 28, wherein the left ventricular afterload is minimized or reduced by administering a pharmaceutical dosage form comprising nitroglycerin or calcium channel blocker to the patient.

30. The method of claim 28, wherein the left ventricular afterload is minimized or reduced using an intra-aortic balloon pump.

ABSTRACT

The invention relates methods of reducing the risk or preventing the occurrence of an adverse event (AE) or a serious adverse event (SAE) associated with a medical treatment comprising inhalation of nitric oxide.

Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Filer:	Janis K. Fraser/Christine Grace
Attorney Docket Number:	26047-0003011

Filed as Small Entity

Track I Prioritized Examination - Nonprovisional Application under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	70	70
Utility Search Fee	2111	1	300	300
Utility Examination Fee	2311	1	360	360
Request for Prioritized Examination	2817	1	2000	2000
Pages:				
Claims:				
Miscellaneous-Filing:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Publ. Fee- Early, Voluntary, or Normal	1504	1	0	0
PROCESSING FEE, EXCEPT PROV. APPLS.	2830	1	70	70
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**2800**

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Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension
First Named Inventor/Applicant Name:	James S. Baldassarre
Customer Number:	94169
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)

1	TrackOne Request	Track.pdf	160498 6b8f08011feee0f9e03c229a17e5d726affeb653	no	2
Warnings:					
Information:					
2	Transmittal Letter	IDS.pdf	65337 d07cea110e1e4abf2d509b321b3be2c5bac63f96	no	2
Warnings:					
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3	Information Disclosure Statement (IDS) Form (SB08)	23271004.pdf	616505 b49e1163b4d2dd656b55c0e59dfd1a9dceaa7ea8	no	10
Warnings:					
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4	Power of Attorney	POA.pdf	191666 0f272a706786efb93fa958415521c63ba73ac2f8	no	3
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5	Oath or Declaration filed	Declaration.pdf	111812 f4c42defa1bea780688d0b4cf07bdd1a1fab5205	no	2
Warnings:					
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6	Transmittal of New Application	Transmittal.pdf	98643 6156367f75a2e8cabb8b77252b15224a94023e17	no	3
Warnings:					
Information:					
7	Application Data Sheet	ADS.pdf	1561779 32b5d06c666aaffb7ca1fa42df2fc000ff78d190	no	8
Warnings:					
Information:					
8		Application.pdf	3048740 e75b44c4da15a405c10ef8fc42e4920ba8622426	yes	29

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	22
Claims	23	28

	Abstract		29	29	
Warnings:					
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9	Fee Worksheet (SB06)	fee-info.pdf	40541 36d9bf4b373f9f577cf10e936818cae426f6a8f5	no	2
Warnings:					
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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Doc Code: TRACK1.REQ
Document Description: TrackOne Request

PTO/AIA/424 (03-14)

CERTIFICATION AND REQUEST FOR PRIORITIZED EXAMINATION UNDER 37 CFR 1.102(e) (Page 1 of 1)

First Named Inventor:	James S. Baldassarre	Non provisional Application Number (if known):	
Title of Invention:	Methods of Treating Term and Near-Term Neonates Having Hypoxic Respiratory Failure Associated with Clinical or Echocardiographic Evidence of Pulmonary Hypertension		

APPLICANT HEREBY CERTIFIES THE FOLLOWING AND REQUESTS PRIORITIZED EXAMINATION FOR THE ABOVE-IDENTIFIED APPLICATION.

1. The processing fee set forth in 37 CFR 1.17(i)(1), the prioritized examination fee set forth in 37 CFR 1.17(c), and if not already paid, the publication fee set forth in 37 CFR 1.18(d) have been filed with the request. The basic filing fee, search fee, and examination fee are filed with the request or have been already been paid. I understand that any required excess claims fees or application size fee must be paid for the application.

2. I understand that the application may not contain, or be amended to contain, more than four independent claims, more than thirty total claims, or any multiple dependent claims.

3. The applicable box is checked below:

I. ☒ Original Application (Track One) - Prioritized Examination under § 1.102(e)(1)

i. (a) The application is an original non provisional utility application filed under 35 U.S.C. 111(a). This certification and request is being filed with the utility application via EFS-Web.

---OR---

(b) The application is an original non provisional plant application filed under 35 U.S.C. 111(a). This certification and request is being filed with the plant application in paper.

ii. An executed inventor's oath or declaration under 37 CFR 1.63 or 37 CFR 1.64 for each inventor, **or** the application data sheet meeting the conditions specified in 37 CFR 1.53(f)(3)(i) is filed with the application.

II. ☐ Request for Continued Examination - Prioritized Examination under § 1.102(e)(2)

i. A request for continued examination has been filed with, or prior to, this form.
ii. If the application is a utility application, this certification and request is being filed via EFS-Web.
iii. The application is an original non provisional utility application filed under 35 U.S.C. 111(a), or is a national stage entry under 35 U.S.C. 371.
iv. This certification and request is being filed prior to the mailing of a first Office action responsive to the request for continued examination.
v. No prior request for continued examination has been granted prioritized examination status under 37 CFR 1.102(e)(2).

Signature /Janis K. Fraser/	Date August 7, 2014
Name (Print/Typed) Janis K. Fraser, Ph.D., J.D.	Practitioner Registration Number 34,819

Note: *This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. Submit multiple forms if more than one signature is required.**

☒ *Total of 1 forms are submitted.

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The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant *(i.e.,* GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre
Serial No.	:	Not Yet Assigned
Filed	:	Herewith
Title	:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

MAIL STOP AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

INFORMATION DISCLOSURE STATEMENT

Please consider the references listed on the enclosed PTO-SB-08 Form. Under 35 USC §120, this application relies on the earlier filing date of application serial numbers 12/494,598, filed on June 30, 2009; 12/820,866, filed on June 22, 2010; 12/821,041, filed on June 22, 2010; 13/651,660, filed on October 15, 2012; 13/683,417, filed on November 21, 2012; 13/683,444, filed on November 21, 2012; and 14/451,057, filed on August 4, 2014. The cited references were submitted to and/or cited by the Office in the prior applications and therefore are not provided in this application.

Applicant wishes to bring to the Examiner's attention the following related U.S. applications:

- USSN 12/494,598, filed June 30, 2009, abandoned (attorney docket no. 26047-0003001);
- USSN 12/820,866, filed June 22, 2010, abandoned (attorney docket no. 26047-0003002);
- USSN 12/820,980, filed June 22, 2010, abandoned (attorney docket no. 26047-0003003);
- USSN 12/821,020, filed June 22, 2010, Patent No. 8,282,966 (attorney docket no. 26047-0003004);
- USSN 12/821,041, filed June 22, 2010, Patent No. 8,293,284 (attorney docket no. 26047-0003005);
- USSN 13/683,236, filed November 21, 2012 (attorney docket no. 26047-0003006);
- USSN 13/651,660, filed October 15, 2012, Patent No. 8,431,163 (attorney docket no. 26047-0003007);

- USSN 13/683,417, filed November 21, 2012, Patent No. 8,795,741 (attorney docket no. 26047-0003008);
- USSN 13/683,444, filed November 21, 2012 (attorney docket no. 26047-0003009); and
- USSN 14/451,057, filed August 4, 2014 (attorney docket no. 26047-0003010).

The prosecution histories for these applications are available on PAIR, and thus are not provided with this communication. Copies of the prosecution history documents will be supplied if the Examiner requests.

This statement is being filed with the application. Apply any necessary charges or credits to Deposit Account 06-1050, referencing the above attorney docket number.

Respectfully submitted,

Date: August 7, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

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Facsimile: (877) 769-7945

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Doc description: Information Disclosure Statement (IDS) Filed

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	Filing Date	
	First Named Inventor	Baldassarre
	Art Unit	
	Examiner Name	
	Attorney Docket Number	26047-0003011

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Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	2	5651358	A	1997-07-29	Briend	
	3	5873359	A	1999-02-23	Zapol	
	4	6063407	A	2000-05-16	Zapol	
	5	6142147	A	2000-11-07	Head	
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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20020185126	A1	2002-12-12	Krebs	
	2	20030131848	A1	2003-07-17	Stenzler	
	3	20040106954	A1	2004-06-03	Whitehurst	
	4	20090018136	A1	2009-01-15	Oppenheimer	
	5	20090029371	A1	2009-01-29	Elliott	
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	1	EP1682672	EP		2006-07-26			☐

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	Attorney Docket Number	26047-0003011

	2	WO2005004884	WO		2005-01-20			☐
	3	WO2006127907	WO		2006-11-30			☐
	4	WO2010019540	WO		2010-02-18			☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1	Adatia et al., "Inhaled Nitric Oxide and Hemodynamic Evaluation of Patients With Pulmonary Hyptertension Before Transplantation," Journal of the American College of Cardiology, Elsevier, New York, NY, Vol. 25, No. 7, page 1663, June 1, 1995	☐
	2	Advances in Pulmonary Hypertension, Vol. 7(4), pages 1-418, Winter 2008-2009 (entire issue)	☐
	3	Al-Alaiyan et al., "Inhaled nitric oxide in persistent pulmonary hypertension of the newborn refractory to high-frequency ventilation," Crit. Care, Vol. 3, No. 1, pages 7-10 (1999)	☐
	4	Argenziano et al., "Inhaled Nitric Oxide is not a Myocardial Depressant in a Porcine Model of Heart Failure," The Journal of Thoracic and Cardiovascular Surgery, Vol. 115, pages 700-704 (1998)	☐
	5	Atz et al., "Combined Effects of Nitric Oxide and Oxygen During Acute Pulmonary Vasodilator Testing," Journal of the American College of Cardiology (JACC), Vol. 33, No. 3, pages 813-819 (1999)	☐
	6	Atz et al., "Inhaled nitric oxide in the neonate with cardiac disease," Seminars in Perinatology, Vol. 21(5), pages 441-455 (1997)	☐

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	Attorney Docket Number	26047-0003011

	7	AU 2009202685 Office Action dated 06/17/10 (3 pages)	☐
	8	AU 2009202685 Office Action Response dated 07/29/2010, 19 pages	☐
	9	Azeka et al., "Effects of Low Doses of Inhaled Nitric Oxide Combined with Oxygen for the Evaluation of Pulmonary Vascular Reactivity in Patients with Pulmonary Hypertension," Pedatric Cardiol., Vol. 23, pages 20-26 (2002)	☐
	10	Barrington et al., "Inhaled Nitric Oxide for Preterm Infants: A Systematic Review," Pediatrics, Vol. 120; pages 1088-1099, DOI: 10.1542/peds (2007)	☐
	11	Barst et al., "Nitric Oxide in Combination with Oxygen versus Either Oxygen Alone or Nitric Oxide Alone for Acute Vasodilator Testing in Children with Pulmonary Hypertension: A Multicenter, Randomized Study," INO Therapeutics/ Ikaria, Baltimore Convention Center, May 3, 2009, 2 pages, Abstract, downloaded 7/2/2009 from http://127.0.0.1:9080/ PAS09A1/view.y?nu=PAS09L1_1507	☐
	12	Barst et al., "Vasodilator Testing with Nitric Oxide and/or Oxygen in Pediatric Pulmonary Hypertension," Pediatric Cardiology; Published online 20 April 2010, 9 pages	☐
	13	Beggs et al., "Cardiac Failure in Children," 17th Expert Committee on the Selection and Use of Essential Medicines, Geneva, March 2009, 31 pages	☐
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	18	Bichel et al., "Successful weaning from cardiopulmonary bypass after cardiac surgery using inhaled nitric oxide", Pediatric Anaesthesia, Vol. 7, pages 335-339 (1997)	☐
	19	Bin-Nun et al., "Role of iNO in the modulation of pulmonary vascular resistance," Journal of Perinatology, Vol. 28, pages S84-S92 (2008)	☐
	20	Bland, "Pulmonary vascular dysfuction in preterm lambs with chronic lung disease," Am J Physical Lung Cell Mol. Physiol., Vol. 285: L76-L85 (2003)	☐
	21	Bloch et al., Cardiovasc. Res. 2007, "Inhaled NO as a therapeutic agent," Vol. 75(2), pages 339-348 (July 15, 2007)	☐
	22	Bocchi et al.,"Inhaled Nitric Oxide Leading to Pulmonary Edema in Stable Severe Heart Failure," The American Journal of Cardiology, Vol. 74, pages 70-72 (1994)	☐
	23	Bolooki, Clinical Application of the Intra-Aortic Balloon Pump, 3rd Ed., pages 252-253 (1998)	☐
	24	Branson, "Inhaled Nitric Oxide in Adults," The Science Journal of the American Association for Respiratory Care 1997 Open Forum Abstracts, December 7, 1997, 2 pages, retrieved at <<http://www.rcjournal.com/abstracts/1997/?id=A00000929>> on 12/22/2010	☐
	25	Braunwald, Heart Failure, chapter 233 of Harrison's Principles of Internal Medicine, 14th Edition, pages1287-1291 and 1360 (1998)	☐
	26	Bublik et al., "Pediatric cardiomyopathy as a chronic disease: A perspective on comprehensive care programs, Progress in Pediatric," Pediatric Cardiology, Vol. 25, pages 103-111 (2008)	☐
	27	Budts et al., "Residual pulmonary vasoreactivity to inhaled nitric oxide in patients with severe obstructive pulmonary hypertension and Eisenmenger syndrome," Heart, Vol. 86, pages 553-558 (2001)	☐
	28	Canadian Office Action mailed May 31, 2011 for Canadian Patent Application No. 2671029, a counterpart foreign application of US application no. 12/494,598	☐

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	29	Clark et al., "Low-Dose Nitric Oxide Therapy for Persistent Pulmonary Hypertension: 1-Year Follow-up," Journal of Perinatology, Vol. 23, pages 300-303 (2003)	☐
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	31	Cockrill et al., "Comparison of the Effects of Nitric Oxide, Nitroprusside, and Nifedipine on Hemodynamics and Right Ventricular Contractibility in Patients With Chronic Pulmonary Hypertension," CHEST, Vol. 119, No. 1, pages 128-136 (2001)	☐
	32	Comparison of Supplemental Oxygen and Nitric Oxide for Inhalation in the Evaluation of the Reactivity of the Pulmonary Vasculature During Acute Pulmonary Vasodilator Testing, http://clinicaltrials.gov/archive/ NCT00626028/2009_01_12 January 12, 2009	☐
	33	Cornfield et al., "Randomized, Controlled Trial of Low-dose Inhaled Nitric Oxide in the Treatment of Term and Near-term Infants With Respiratory Failure and Pulmonary Hypertension," Pediatrics, Vol. 104, No. 5, pages 1089-1094 (1999)	☐
	34	Cox et al., "Factors Associated with Establishing a Causal Diagnosis for Children with Cardiomyopathy," Pediatrics, Vol. 118, No 4, pages 1519-1531 (2006)	☐
	35	Cujec et al., "Inhaled Nitric Oxide Reduction in Systolic Pulmonary Artery Pressure is Less in Patients with Decreased Left Ventricular Ejection Fraction," Canadian Journal of Cardiology, Vol. 13(9), pages 816-824 (1997)	☐
	36	Cuthbertson et al., "UK guidelines for the use of inhaled nitric oxide therapy in adults ICUs," Intensive Care Med., Vol. 23, Springer-Verlag, pages 1212-1218 (1997)	☐
	37	Davidson et al., "Inhaled nitric oxide for the early treatment of persistent pulmonary hypertension of the term newborn: a randomized, double-masked, placebo-controlled, dose-response, multicenter study," PEDIATRICS, Vol. 101 (3 Pt 1), pages 325-34 (1998)	☐
	38	Davidson et al., "Safety of Withdrawing Inhaled Nitric Oxide Therapy in Persistent Pulmonary Hypertension of the Newborn," Pediatrics, Vol. 104, No. 2, pages 231-236 (1999)	☐
	39	Day et al., "Pulmonary Vasodilatory Effects of 12 and 60 Parts Per Million Inhaled Nitric Oxide in Children with Ventricular Septal Defect," The American Journal of Cardiology, Vol. 75, pages 196-198 (1995)	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	Examiner Name	
	Attorney Docket Number	26047-0003011

	40	Definition of Contraindication on Medicine.net.com; http://www.medterms.com/script/main/art.asp?articlekey=17824; retrieved 3/14/2011; 2 pages	☐
	41	Delivery of Inhaled Nitric Oxide Therapy through an Adult or Pediatric Nasal Cannula, Reference: UTMB RESPIRATORY CARE SERVICES Reviewed: 05/31/05	☐
	42	Dickstein et al., "A Theoretic Analysis of the Effect of Pulmonary Vasodilation on Pulmonary Venous Pressure: Implications for Inhaled Nitric Oxide Therapy," The Journal of Heart and Lung Transplant, pages 715-721 (1996)	☐
	43	Dorland, "The American Illustrated Medical Dictionary," 7th edition, W.B. Saunders Company, page 113 (1914)	☐
	44	Dorling, "Neurodevelopmental outcome following Nitric Oxide Therapy for Persistent Pulmonary Hypertension in Term Newborn Infants," Neonatal Intensive Care Unit, Leicester Royal Infirmary, 8/8/2003, modified 11/12/2003, 3 pages	☐
	45	Douwes et al., "The Maze of Vasodilator Response Criteria," Published online: 26 November 2010, Pediatr. Cardiol., Vol. 32, pages 245-246 (2011)	☐
	46	Ehrenkranz, "Inhaled Nitric Oxide in Full-Term and Nearly Full-Term Infants with Hypoxic Respiratory Failure," The Neonatal Inhaled Nitric Oxide Study Group, N. Engl. J. Med., Vol. 336, No. 9, pages 597-605 (1997)	☐
	47	http://www.cc.nih.gov/ccmd/clinical_services.html, page last updated May 19, 2011	☐
	48	http://www.medterms.com/script/main/art.asp?articlekey=17824, Definition of Contraindication, last Editorial Review March 19, 2012	☐
	49	Elbl et al., "Long-term serial echocardiographic examination of late anthracycline cardiotoxicity and its prevention by dexrazoxane in paediatric patients," Eur. J. Pediatr., Vol. 164, pages 678-684 (2005)	☐
	50	EP 09251949 Office Action dated 10/11/2010, 5 pages	☐

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
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	First Named Inventor	Baldassarre
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	First Named Inventor	Baldassarre
	Art Unit	
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CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Janis K. Fraser/	Date (YYYY-MM-DD)	2014-08-07
Name/Print	Janis K. Fraser	Registration Number	34819

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these record s.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PTO/AIA/82A (07-13)
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TRANSMITTAL FOR POWER OF ATTORNEY TO ONE OR MORE REGISTERED PRACTITIONERS

NOTE: This form is to be submitted with the Power of Attorney by Applicant form (PTO/AIA/82B) to identify the application to which the Power of Attorney is directed, in accordance with 37 CFR 1.5, unless the application number and filing date are identified in the Power of Attorney by Applicant form. If neither form PTO/AIA/82A nor form PTO/AIA82B identifies the application to which the Power of Attorney is directed, the Power of Attorney will not be recognized in the application.

Application Number	Not Yet Assigned
Filing Date	Herewith
First Named Inventor	James S. Baldassarre
Title	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION
Art Unit	
Examiner Name	
Attorney Docket Number	26047-0003011

SIGNATURE of Applicant or Patent Practitioner

Signature	/Janis K. Fraser/	Date (Optional)	August 7, 2014
Name	Janis K. Fraser, Ph.D., J.D.	Registration Number	34,819
Title (if Applicant is a juristic entity)			
Applicant Name (if Applicant is a juristic entity)			

NOTE: This form must be signed in accordance with 37 CFR 1.33. See 37 CFR 1.4(d) for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ *Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**
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If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

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POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

94169

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter to:

☐ The address associated with the above-mentioned Customer Number

OR

☒ The address associated with Customer Number: **94169**

OR

Firm or Individual Name					
Address					
City		State		Zip	
Country					
Telephone		Email			

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

INO Therapeutics LLC

☐ Inventor or Joint Inventor (title not required below)

☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)

☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)

☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature		Date (Optional)	7/21/14
Name	William Scheinler		
Title	Associate General Counsel		

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ *Total of 1 forms are submitted.

PTO/AIA/82C (07-13)
Approved for use through 11/30/2014. OMB 0651-0051
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POWER OF ATTORNEY BY APPLICANT

No more than ten (10) patent practitioners total may be appointed as set forth below by name and registration number. This page need not be submitted if appointing the Patent Practitioner(s) associated with a Customer Number (see form PTO/AIA/82B):

Name	Registration Number

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

First Named Inventor	:	James S. Baldassarre
Serial No.	:	Not Yet Assigned
Filed	:	Herewith
Title	:	METHODS OF TREATING TERM AND NEAR-TERM NEONATES HAVING HYPOXIC RESPIRATORY FAILURE ASSOCIATED WITH CLINICAL OR ECHOCARDIOGRAPHIC EVIDENCE OF PULMONARY HYPERTENSION

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

SUBMISSION OF DECLARATION

The attached declaration of inventor James S. Baldassarre is a copy of his declaration filed in a parent application, U.S. serial no. 14/451,057. The present application is a continuation of U.S. serial no. 14/451,057.

Respectfully submitted,

Date: August 7, 2014

/Janis K. Fraser/
Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Customer Number 94169
Fish & Richardson P.C.
Telephone: (617) 542-5070
Facsimile: (877) 769-7945

23270592.doc

Attorney Docket No. 26047-0003007

PTO/AIA/01 (06-12)
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)

Title of Invention	METHODS OF REDUCING THE RISK OF OCCURRENCE OF PULMONARY EDEMA ASSOCIATED WITH INHALATION OF NITRIC OXIDE GAS

As the below named inventor, I hereby declare that:

This declaration is directed to:

☒ The attached application, or

☐ United States application or PCT international application number _____

filed on _____

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

WARNING:

Petitioner/applicant is cautioned to avoid submitting personal information in documents filed in a patent application that may contribute to identity theft. Personal information such as social security numbers, bank account numbers, or credit card numbers (other than a check or credit card authorization form PTO-2038 submitted for payment purposes) is never required by the USPTO to support a petition or an application. If this type of personal information is included in documents submitted to the USPTO, petitioners/applicants should consider redacting such personal information from the documents before submitting them to the USPTO. Petitioner/applicant is advised that the record of a patent application is available to the public after publication of the application (unless a non-publication request in compliance with 37 CFR 1.213(a) is made in the application) or issuance of a patent. Furthermore, the record from an abandoned application may also be available to the public if the application is referenced in a published application or an issued patent (see 37 CFR 1.14). Checks and credit card authorization forms PTO-2038 submitted for payment purposes are not retained in the application file and therefore are not publicly available.

LEGAL NAME OF INVENTOR

Inventor: James S. Baldassarre Date (Optional): October 8, 2012

Signature: /James S. Baldassarre/

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form. Use an additional PTO/AIA/01 form for each additional inventor.

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 14/454,373	Filing Date 08/07/2014	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)		
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)
☒ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	**70**
☒ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	**300**
☒ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	**360**
TOTAL CLAIMS (37 CFR 1.16(i))	30 minus 20 =	* 10	x $40 =	**400**
INDEPENDENT CLAIMS (37 CFR 1.16(h))	4 minus 3 =	* 1	x $210 =	**210**
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	**1340**

APPLICATION AS AMENDED – PART II

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))						
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
					TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LDRC
/EVA GILLIS/